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a "diagnostic map" that's hard to read

The symptoms of classical myxedema actually provide only a few sign posts in the vast territory of hypothyroidism. To find the path of correct treatment, "a high degree of suspicion for thyroid disorder remains the most important factor in diagnosis of any case."[1]

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References: **1.** Pickering, D. E., and Lusted, L. B.: GP *11*:99 (Feb.) 1955. **2.** Perloff, W. H.: J.A.M.A. *157*:651 (Feb.) 1955. **3.** Watson, B. A.: New York State J. Med. *54*:2045 (July 15) 1954. **4.** Panos, T. C.: South. M. J. *48*:527 (May) 1955.

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TODAY'S THYROIDOLOGISTS AND THEIR BECKONING FRONTIERS*

RULON W. RAWSON, M.D.†

The Division of Clinical Investigation, Sloan-Kettering Institute and Department of Medicine, Memorial Hospital, New York, N. Y.

DURING the past one and a half decades, our knowledge of thyroid physiology in health and disease has increased at an unprecedented rate. Many of the reports of this newer knowledge of thyroidology have been presented before the annual meetings and published in the Transactions of this Association. This renaissance in thyroidology might be attributed to many factors. One important reason is the availability of modern tools of study which have been developed in the laboratories of physicists, physical chemists and organic chemists. They have made it feasible to approach many previously unanswerable problems with workable methods. Studies with radioactive iodine have made it possible to investigate various functions of the thyroid in physiologic equilibrium. The availability of thyroid inhibiting drugs which interfere with the production of thyroid hormones has facilitated the separation and definition of certain steps in the synthesis of thyroid hormones. With newly available chromatographic technics combined with isotopic and other physical chemical methods, it has been possible not only to isolate and identify previously unidentified iodinated compounds in the thyroid and serum but also to identify the proteins by which they are transported in

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* *Presidential Address*, presented at the Annual Meeting of the American Goiter Association, Chicago, Illinois, May 3–5, 1956.

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† Professor of Medicine, Cornell University Medical College.

the circulation. With these techniques, it has also been possible to identify certain metabolites of the thyroid hormones. Probably the most important reason for the rapid and continuous growth in our knowledge of the thyroid is the fact that knowledgeable, imaginative and enthusiastic investigators from many and varied disciplines have been attracted by the problems of normal and morbid thyroid physiology. Today the American Goiter Association, a society originally founded to study problems of thyroidology, has as members biophysicists, biochemists, physiologists and clinical investigators who have joined with the surgeons, physicians and pathologists in studying the many challenging problems of normal and morbid thyroid physiology.

From the practical point of view, this new knowledge of the thyroid has made it possible for those of us who are interested in correcting the abnormalities of disease to approach certain diseases of the thyroid with therapeutic programs which are not only more rational but more effective in treating our patients. Notwithstanding the fact that our modern methods of therapy are much more satisfying to both patient and physician, there remain many unanswered and newly presented questions concerning classic diseases of the thyroid. Some of the major questions which face us concerning these diseases are listed in Table 1. Answers to these questions would, undoubtedly, lead to improved treatment of thyroid disorders and might even lead to methods of preventing some of these maladies. Such problems constitute some of the beckoning frontiers in thyroidology for clinicians, who undoubtedly will require the help of their colleagues in the basic sciences. To discuss adequately each of these problems demanding imaginative research could occupy the full time of this meeting.

The beckoning frontiers that I wish to develop in the next few minutes are timely and have to do with the known thyroid hormones and their metabolites and their possible roles in the body economy in health and disease.

Until a few years ago we thought of thyroxine, which was isolated from the thyroid in 1915 by Kendall (1) and synthesized in 1927 by Harington (2), as the only thyroid hormone. However, in 1951 and 1952 Gross and Pitt-Rivers (3, 4, 5) isolated 3:5:3′-triiodothyronine from the serum and Roche, Lissetzky and Michel (6) demonstrated it in the thyroid gland.

Subsequent studies made by Roche and Michel (7, 8) and their associates resulted in the isolation and identification of thyroxine, 3:5:3′-triiodothyronine, 3:3′:5′-triiodothyronine and 3:3′-diiodothyronine from the thyroids and sera of rats (Fig. 1). The three latter iodinated compounds differ from thyroxine only by the degree and sites of iodination. The 5 and

Table 1. Problems and questions in thyroid disease on the research

Graves' Disease
- Etiologic factors
  - Psychogenic
  - Trauma
  - Infection
  - Nutrition
  - Peripheral tissues
  - Thyroid-stimulating hormone (TSH)
  - Other endocrines
- Identification of thyroid hormones and metabolites
- Mechanism of exophthalmos
  - Thyroid hormone vs. thyroid-stimulating hormone vs. exophthalmos-producing substance
- Cardiac changes
- Thymicolymphadenopathy
- Muscle symptoms
- Gynecomastia
- Joint symptoms

Hyperfunctioning Adenoma
- Etiologic factors
- Identification of thyroid hormones and metabolites
- Mechanism of cardiotoxicity

Benign Non-toxic Goiters
- Etiologic factors
- Hormones elaborated
- Prognostic fate

Cancer of the Thyroid
- Etiologic factors
- Metastatic patterns and pathways
  - Relationship to treatment
- Factors influencing host's response
- Factors influencing pattern of function

Myxedema and Cretinism
- Etiologic factors
- Mechanisms of change in metabolism and nutrition
- Cardiovascular system
- Hematopoiesis
- Other endocrines
- Growth and maturation
- Cerebral development and function

Thyroiditis (Hashimoto's, Riedel's, suppurative, acute nonsuppurative)
- Etiologic factors
- Natural course
- Effects of function of thyroid

5′ positions are the sites of variation. Roche and his associates (9, 10) also demonstrated that certain metabolites of the thyroid hormones can be recovered from various tissues. These metabolites may show changes in the distribution of iodine but they may also show changes in the alanine side-chain. There may be a loss of the amino group, with or without change

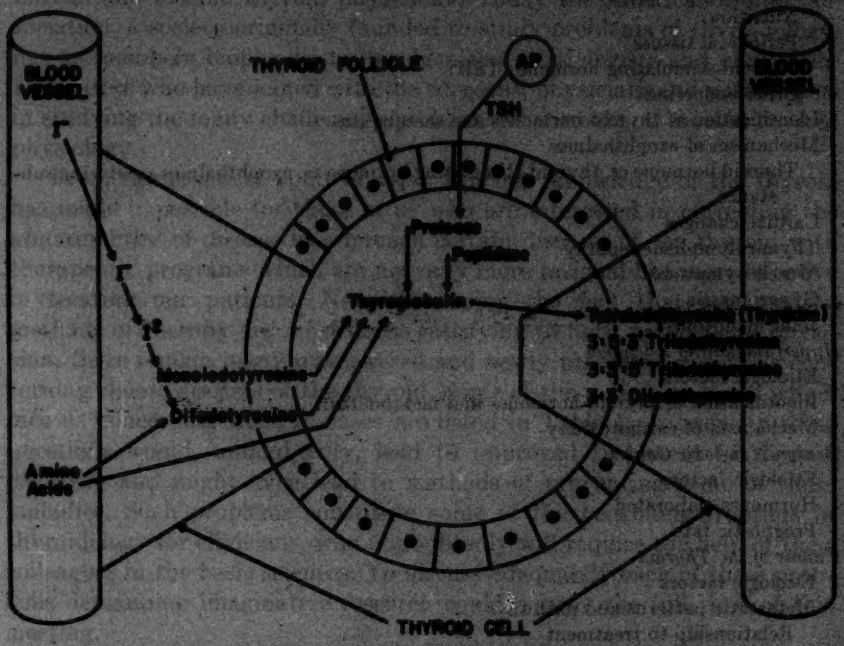

FIG. 1. Functions of the thyroid—Today's concept. On the left are illustrated the known steps in synthesis of thyroglobulin. Thyroglobulin is hydrolyzed to release thyroid hormones by protease and peptidase which are activated by TSH. On right of diagram are four thyroid hormones which have been identified in thyroid and serum.

or loss of the alpha carbon atom. Many of these observations have been confirmed or extended by Dr. Jamshed Tata. Thus the pyruvic-acid derivatives of thyroxine and triiodothyronine have been recovered from the bile (11). Roche and Michel have recovered triiodothyroacetic acid and 3:3′-diiodothyronine from the kidney (10). Tata has identified 3:5:3′-triiodothyronine, tetraiodothyropropionic acid and/or tetraiodothyroacetic acid and triiodothyropropionic acid and/or triiodothyroacetic acid as metabolites of thyroxine from slices of muscle, kidney and brain (Table 2).

Of these compounds only thyroxine and triiodothyronine have been

demonstrated in humans (12, 13). Needless to say, any final definition of the role of the newly identified agents in human physiology will await their demonstration in the thyroids, sera or peripheral tissues of human subjects.

By applying the techniques with which these compounds have been demonstrated in rat thyroids and sera, it may be possible to demonstrate

TABLE 2.—THYROID HORMONES AND THEIR METABOLITES WHICH HAVE BEEN IDENTIFIED IN THYROID, SERUM, BILE, TISSUES, OR URINE

COMPOUND	STRUCTURAL FORMULA	THYROID	SERUM	BILE	TISSUES	URINE
		+	+	+[a]	+	+
3-5-3' Triiodothyronine		+	+	+	+	
3-3'-5' Triiodothyronine		+	+			
3-5' Diiodothyronine		+	+	+	+	
3-5-3' Triiodothyronine Acid				+	+	+
3-3'-5' Triiodothyronine Acid				+		+
3-5-3' Triiodothyronine Acid					+	
3-3'-5' Triiodothyronine Acid						
3-5-3' Triiodothyronine Acid					+[a]	
3-3'-5' Triiodothyronine Acid					+[a]	

these or other iodinated thyronines in patients with abnormal thyroids. Stanbury and associates (14) have already reported the recovery of monoiodotyrosine and diiodotyrosine from the serum of a goitrous young male with hypothyroidism. Such observations should encourage us to look at various goitrous states with the hope of identifying abnormal patterns of hormonal metabolism. At last year's meeting of this association, Dr. Jacob Robbins (15) described an unknown iodinated protein that he had recovered from the sera of certain patients with functioning cancers of the

thyroid. At this meeting you have heard Dr. [illegible] compound can be separated from albumin, that it has a molecular weight of about 60,000, and that on enzymatic digestion it yields monoiodotyrosine and probably 3:3′-diiodothyronine or possibly thyronine.

Imaginative physiologists and clinicians will naturally be interested in defining any differences in the physiologic effects of these various iodinated thyronines and their metabolites. Preliminary studies made in laboratory animals indicate that some of these compounds differ not only quantitatively but qualitatively in their physiologic effects at given dosage levels.

Whereas 3:5:3′-triiodothyronine is two to five times more active than thyroxine by all of the criteria used—basal metabolic rate, goiter prevention, inhibition of thyroidal uptake of I^{131}, suppression of pituitary thyrotropic activity and the promotion of metamorphosis—certain metabolites of thyroxine and of triiodothyronine differ qualitatively at given dosage levels. For example, triiodothyroacetic acid is comparatively weak in preventing the development of a goiter and triiodothyroacetic acid and triiodothyropropionic acid are weak in enhancing the rate of oxygen consumption in either the rat or the phosphate-loaded dog, but they are both much more effective than thyroxine or triiodothyronine in promoting metamorphosis in the tadpole (Table 3).

Examination of Table 3 reveals that there remain many other studies to be made in defining the quantitative and qualitative differences in the effects of these hormones and their metabolites on thyroid and pituitary function, body metabolism, and growth in experimental animals.

TABLE 3. COMPARISON OF VARIOUS PHYSIOLOGIC EFFECTS OF THYROXINE AND OTHER THYROID HORMONES OR THEIR METABOLITES AS DETERMINED IN LABORATORY ANIMALS

(It is to be noted that complete studies with many of these compounds have not been made)

	Oxygen consumption	Goiter prevention	Suppression of I^{131} uptake	Pituitary TSH	Oxygen consumption with PO_4 load	Metamorphosis
L-Thyroxine	1	1	1	1		1
D-Thyroxine		0.1				<0.05
3:5:3′ Triiodothyronine		5	2–5	5	5	5
3:3′:5′ Triiodothyronine						
3:3′ Diiodothyronine		0.2*				0.7*
3:5:3′ Triiodothyropyruvic Acid		trace*				
3:5:3′:5′ Tetraiodothyropyruvic Acid		trace*				
3:5:3 Triiodothyroacetic Acid		0.1†	0.25–0.5		<0.25	25
3:5:3′:5′ Tetraiodothyroacetic Acid			0.25–0.5			50
3:5:3′ Triiodothyropropionic Acid	<0.15	1.0*	0.25		<0.25	200
3:5:3′:5′ Tetraiodothyropropionic Acid		0.7†	0.15			50

* Roche *et al.*
† Pitt-Rivers.

[illegible]

What Role Do the Thyroid Hormones Play in:

I. Metabolism
- Carbohydrate
- Fat
- Cholesterol and steroids
- Nitrogen
  - Serum proteins
  - Amino acids
  - Creatine
  - Nucleic acid
- Enzymes
  - Oxidases
  - Esterases
  - Carbohydrases
  - Cathepsins
  - Amidases
  - Transferases
- Phosphate

II. Organ Systems
- Cardiac
- Nervous
- Renal
- Gastro-intestinal
- Endocrines

III. Immune Mechanisms

Table 4 lists a variety of metabolic systems known to be altered by thyroidectomy or by the administration of thyroxine or desiccated thyroid (16). To determine any qualitative or quantitative differences in the effects of the newly isolated thyroid hormones or their metabolites on any of these systems known to be influenced by altered states of thyroid function would be an arduous but important and fruitful project for biochemists interested in the metabolic effects of thyroid hormones.

The mechanisms by which thyroxine or other thyroid hormones exert their actions are far from being clear. Since generalized metabolic changes are induced by minimal (10^{-7} M) concentrations of thyroxine in the body fluids, it has been tempting to consider that this hormone acts either as a catalyst on a fundamental reaction or as a co-enzyme for many reactions. It has been suggested that all oxygen consumption and, indirectly, various metabolic processes are regulated by the effect of thyroxine on cytochrome C (17).

Lardy (18) in a recent review has advanced the suggestion that thyroxine might regulate metabolic rates by varying the efficiency with which cellular oxidations are coupled with phosphorylation. This theory is based on the following premises: a) A relatively high percentage of the total free energy which would ordinarily be liberated by the oxidative reactions is trapped in the form of high-energy phosphate compounds, which are formed from inorganic phosphate. b) The phosphate and high-energy

phosphate compounds are involved in the scheme of electron transport. Two to four moles of phosphate are fixed per mole of oxygen consumed. c) The phosphate compounds formed are the main source of energy for the various forms of work accomplished by the cell. d) The respiratory metabolism of isolated mitochondria, and presumably of tissues *in vivo*, is controlled in large part by the availability of inorganic phosphate and phosphate acceptors. Lardy and others have observed that mitochondrial preparations, when incubated with an oxidisable substrate and necessary co-factors—a phosphate buffer, phosphate acceptors and thyroxine—bind more phosphate than such preparations not exposed to thyroxine. However, since the oxygen consumption increases more rapidly than the phosphate fixed, Lardy suggests that gains in oxygen consumption through the influence of thyroxine are at the expense of cellular efficiency.

There are certain disadvantages of this theory which merit comment. For example, these same changes can be produced by dinitrophenol, *d*-thyroxine, and halides such as iodide or bromide (19, 20). It has been suggested, more recently, that this *in vitro* action of thyroxine is concerned with the control of some structural property rather than the direct interaction of the hormone with the enzymes of oxidative phosphorylation (21). Finally the concentration of hormone required to produce such *in vitro* effects is many times that of hormones observed in the serum in severe hyperthyroidism.

Dr. Roberts and associates have reported at this meeting that the toxicity of triiodothyronine in dogs is readily demonstrable only after administering a phosphate load. It would be of interest to determine if their observations could be related to Dr. Lardy's theory. Their observations would fit more with the observations of Klemperer (22), who observed that the addition of triiodothyronine to mitochondrial preparations in appropriate media increased the incorporation of P^{32} into the A.T.P. system and its rate of turnover. The latter observation might explain the marked and rapid urinary loss of phosphorus seen in myxedematous patients treated with either triiodothyronine or thyroxine (Fig. 2).

Certainly continued studies on the effect of various thyroid hormones and their metabolites on cellular respiration and physiology are indicated. Clarification of the mechanisms of action of these hormones awaits continued and extended studies by the enzymologists.

When one considers the many and varied manifestations of human myxedema and the fact that several thyroid hormones have now been isolated, one naturally asks whether or not these agents might have qualitatively different effects on the various manifestations of hypothyroidism.

In some of our assays of these hormones in human myxedema we have carried out metabolic balance studies and have followed the fate of nitro-

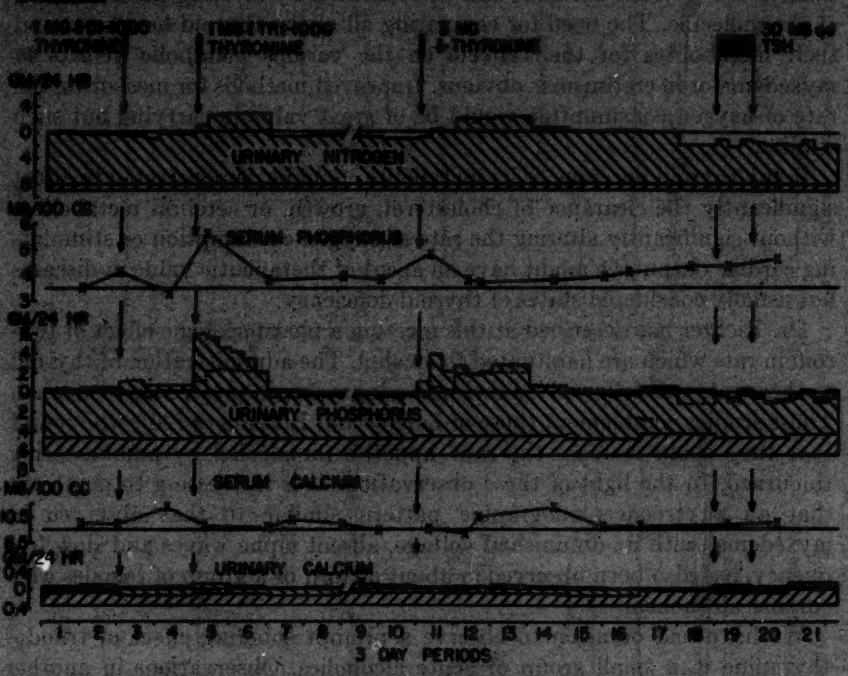

FIG. 2. Urinary excretion of phosphorus and nitrogen in myxedematous female after intravenous administration of *l*-3:5:3′ triiodothyronine and after administration of *l*-thyroxine. The broken line covering phosphorus data represents theoretical phosphorus excretion calculated from urinary nitrogen and calcium. It is to be noted that the actual excretion of phosphorus exceeds the calculated phosphorus.

sequent experience in treating myxedema reveals that the maintenance dose of triiodothyronine is a quarter to a third that of thyroxine.

One year ago Lerman and Pitt-Rivers (24) reported that following the administration of triiodothyroacetic acid (triac) to 2 myxedematous patients in dosages up to 1 and 4 mg. daily there was no rise in the basal metabolic rate but the myxedematous appearance of the patient cleared up, and there was a significant fall in the serum cholesterol level. We (25)

have also observed that one 5-mg. dose of triac, when given intravenously to a myxedematous patient, failed to cause either an immediate or a delayed increase in oxygen consumption. However, this dose of triac did cause a significant increase in urinary nitrogen, phosphorus, sodium, chloride and potassium and a fall in the level of serum cholesterol (Fig. 3). A 15-mg. dose of this agent caused a rise in oxygen consumption. If these observations can be confirmed, we shall have evidence that certain actions of the thyroid hormone can be separated by altering the side-chain of the molecule. The need for comparing all of the thyroid hormones and their metabolites for their effects on the various metabolic defects in myxedema or in cretinism is obvious. Improved methods for measuring the rate of oxygen consumption would be of great value in carrying out such studies.

If any thyroid hormone or its metabolite could be demonstrated to affect significantly the clearance of cholesterol, growth, or cerebral metabolism without significantly altering the rate of oxygen consumption or stimulating cardiac output we might have an agent of therapeutic value in diseases not usually considered states of thyroid deficiency.

Dr. Richter has described at this meeting a pharmacologic effect of thyroid in rats which are habituated to alcohol. The administration of thyroid to these rats was followed by their choosing water in preference to alcohol. These studies complement those of Zarrow and Rosenberg (26), who found that they could increase the rats' appetite for alcohol by administering thiouracil. In the light of these observations it is interesting to point out that an electroencephalographic pattern similar to that observed in myxedema, with its diminished voltage, absent alpha waves and slow frequency, has also been observed in about a third of a group of females with chronic alcoholism.

We have had occasion to observe a prompt sobering effect of triiodothyronine in a small group of acute alcoholics. Observations in another small group of chronic alcoholics are too complicated to evaluate. Certainly, if one of the thyroid hormones proved to have a beneficial effect on theopsyche or possible metabolic defects of the unfortunate alcoholic, many of our 4,500,000 alcoholics might be helped.

Although we usually think of the myxedematous patient as a placid, slow, but pleasant and "gemütlich" individual, it is interesting to quote from the Report on Myxoedema by the Committee of the Clinical Society of London (27): "Delusions and hallucinations occur in nearly half of the cases where the disease is advanced. Insanity as a complication is noted in about the same proportion. It takes the form of acute or chronic mania, dementia or melancholia with a marked predominance of suspicion and self-accusation." In the modern literature, (28, 29, 30), there are several

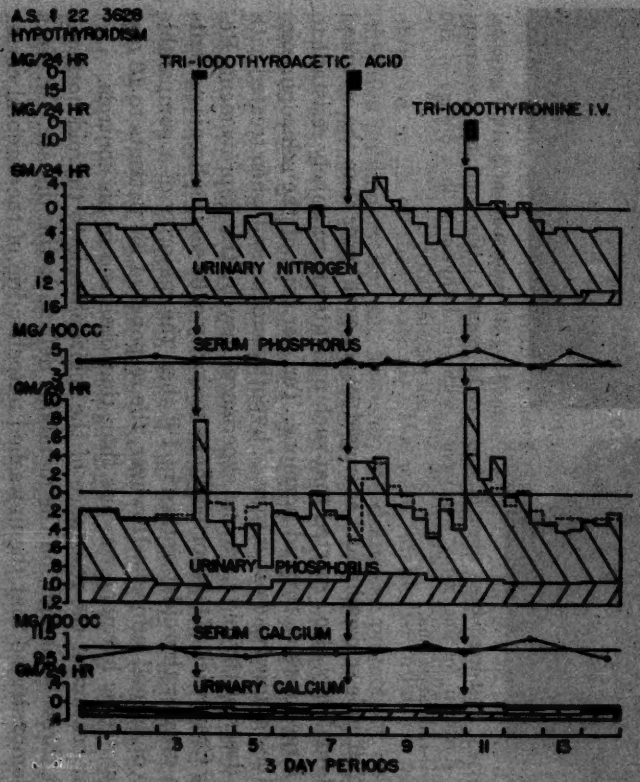

FIG. 3a. Urinary nitrogen and phosphorus observed in hypothyroid male following intravenous administration of triiodothyroacetic acid in doses of 5 mg. and 15 mg. and after administration of triiodothyronine in dose of 1 mg.

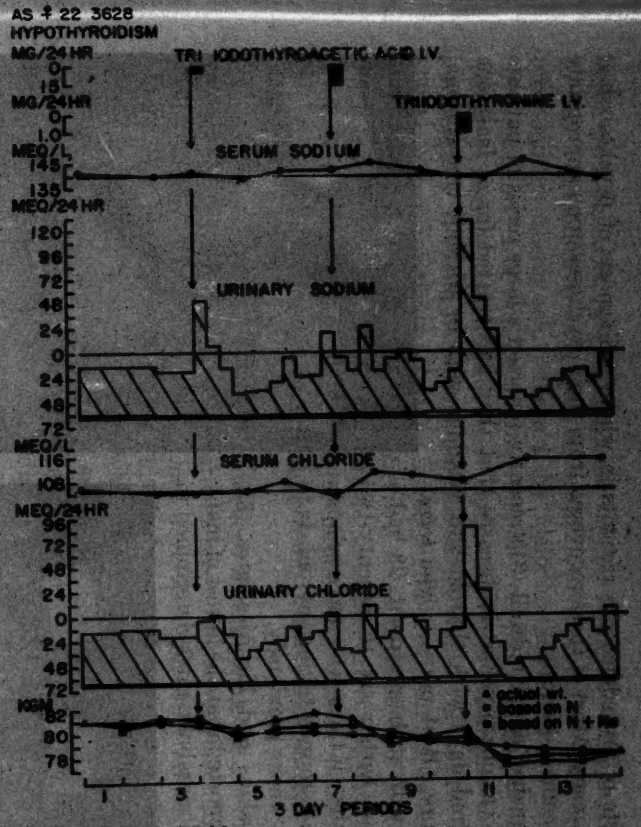

FIG. 3b. Urinary sodium and chloride observed in hypothyroid male after intravenous administration of triiodothyroacetic acid in doses of 5 mg. and 15 mg. and after administering triiodothyronine in a dose of 1 mg.

reports of myxedematous patients in whom a diagnosis of psychosis had been made. Most of these recovered from their psychoses upon appropriate replacement therapy.

Danziger and Knidwall (31) recently reported a large series of patients with various psychiatric diseases that they had treated for at least one hundred days with thyroid and vitamins with or without conventional therapy. Of 91 patients who recovered with such treatment, 28 had a relapse within six to seventy-two months. Of those who had a relapse, 26 had stopped taking thyroid six to eight weeks previously.

Hoskins and his associates (32, 33) reported that the lowest of many basal metabolic rates determined in

FIG. 4a. Post-irradiation ulcer of four years' duration folloing x-ray treatment for basal-cell carcinoma.

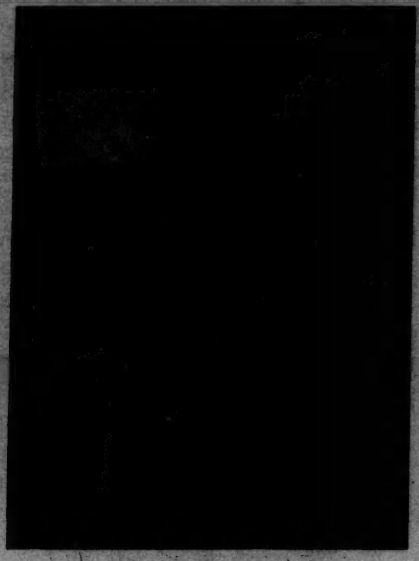

FIG. 4b. Same patient as in Figure 4a, eight months after continued treatment with triiodothyronine in a dosage of 200 micrograms daily.

over 200 male schizophrenics averaged 19 per cent lower than the accepted standard. They also reported that such patients are relatively resistant to even large doses of thyroid hormone. Ten per cent of the schizophrenics that they studied had other signs of hypothyroidism and when treated with large doses of thyroid hormone experienced psychiatric improvement. Recently Cranswick (34) reported that a majority of 31 schizophrenic patients had a greater thyroidal uptake of I^{131} than the majority of a comparable group of normal subjects. However, the response of his patients to 10 mg. of thyrotropic hormone was less than that observed in his controls.

Clarification of the resistance of the schizophrenic to thyroid hormone might throw some light on the metabolic defects in this disease. Dr. Tata has demonstrated that the unwashed mitochondria of the cerebral cortex

taken from chickens, rats and dogs are capable of metabolising thyroxine to 3:5:3′-triiodothyronine, and to tetraiodothyropropionic acid and/or tetraiodothyroacetic acid, followed by deiodination to 3:5:3′-triiodothyropropionic acid and/or 3:5:3′-triiodothyroacetic acid and finally to iodide. If normal human brain tissue can be shown to metabolize thyroxine similarly, it would be most important to determine whether the brain of schizophrenic patients is lacking in this metabolic factor. It would also be most desirable to determine the effects of these metabolites of thyroxine on the total metabolism in schizophrenic and other psychotic patients. I would suggest that one of our major national medical problems, *i.e.*, mental health, offers a challenging and possibly fruitful beckoning frontier to the thyroidologist.

During the past three years we have been investigating the pharmacologic effects of triiodothyronine in patients presenting advanced cutaneous and subcutaneous changes which had developed following intensive x-radiation for neoplastic diseases. This study was excited by an observation made on a 19-year-old youth who in infancy had been treated with x-rays directed at the upper mediastinum for an "enlarged thymus." Cancer of the thyroid developed, which metastasized to the lungs. In an attempt to induce function in his pulmonary metastases, we deprived him of his thyroid and induced myxedema. In the myxedematous state, minimal but characteristic skin changes of radiation appeared over the manubrium, with atrophy, depigmentation and telangiectasia. These changes disappeared on restoring the patient to a euthyroid state and recurred when we allowed him to return to the myxedematous state. We have now treated 27 patients presenting chronic radiation changes in the skin with triiodothyronine in daily doses up to 0.2 mg. Healing of ulcers, softening of the thickened subcutaneous tissues or decrease in telangiectasia was observed in 25 of these patients. We were unable to influence post-irradiation pulmonary fibrosis; however, the decreased pulmonary reserves of these patients made it impossible for us to give the same doses of triiodothyronine that we give to patients whose problems are limited to the skin. We have observed that the topical application of an ointment containing a very small concentration (0.001 per cent) of triiodothyronine causes marked relief of the discomfort complained of by patients with acute radiation dermatitis. These studies might be extended to include the effects of thyroid hormones on wound and burn healing. They also suggest that the effects of these hormones might profitably be investigated for their effects on the skin and its supporting structures or on certain dermatologic ailments.

When one considers that radiation changes in skin, bone or marrow are often followed by neoplastic changes, one might ask if one of the thyroid

hormones or metabolites might prevent or even reverse such neoplastic changes. Several studies made in recent years might suggest a tenuous relationship between thyroid function and the development of certain cancers. In 1954 Spencer (35) reported on statistical surveys which suggest that there is an increased incidence of cancer in communities where nontoxic goiter is endemic. Bather and Francks (36) reported that the carcinogenic effect of dibenzanthracene is diminished by the co-administration of thyroxine.

One year ago Sommers (37) reported on an extensive study of endocrine abnormalities observed at autopsy in 207 women who had died of breast cancer. He was able to study the thyroids of 157 of these women. Fifty-nine per cent of these glands were atrophied and weighed 12 Gm. or less. This atrophy could not be attributed to weight loss or cachexia. More than half of these atrophic thyroids presented nodules which he described as "regenerated foetal follicles or microfollicles and fibrosis intermingled with large colloid filled macrofollicles." An additional 13 per cent of the cancer cases presented what he called adenomatous goiters. Eleven per cent presented either primary hyperplasia of the thyroid, single adenomas or thyroiditis. Whereas only 14 per cent of his cancer patients had histologically normal thyroids, 65 per cent of 198 non-cancer patients had normal thyroids. Atrophy of the thyroid was observed in only 22 per cent of his control cases. Sommers suggests an "endocrine dysfunctional sequence of thyroid atrophy, pituitary amphophil increase, ovarian stromal hyperplasia and associated continuous estrogen stimulation of the breast epithelium."

This possible relationship between thyroid failure and the development of breast neoplasms might be supported by the studies of Hamilton, Durbin and Parrott (38). They reported that in Sprague-Dawley rats in which the thyroids had been destroyed with astatine^{211} there was a 40 per cent incidence of mammary tumors within 350 days of administering the radioactive agent which did not concentrate in mammary tissue. Some of these tumors metastasized to the lungs. They reported that in none of their untreated controls did breast tumors develop within 400 days.

In our own institution we have studied the level of serum protein-bound iodine in 23 patients with metastatic carcinoma of the breast prior to hypophysectomy. The incidence of serum iodine levels of 4 gamma per 100 ml. or less was 26 per cent. Only 2 of these patients had serum iodine levels below 3 gamma per 100 ml. (39).

These studies suggest that most of the patients in this small series had normal thyroid function, unless with finer technics we can demonstrate a qualitative abnormality in the hormones secreted or in the metabolism of these hormones by patients with cancer of the breast.

On the other hand Lerman (40) observed a 4 per cent incidence of cancer in 150 cases of myxedema, and a 0.5 per cent incidence in 1,300 patients with hyperthyroidism. Loeser (41) reported that he administers desiccated thyroid in daily doses of 65 to 325 mg. to all of his patients who have had operations for removal of breast or genital cancers. He stated in a recent preliminary report that in only 1 of 16 women with breast cancer (12 had axillary metastases at operation) whom he had treated with thyroid, did metastases develop in a four-year postoperative period. If comparable results could be obtained in 100 women with axillary metastases, it would indeed be most significant.

Such data, though meager and even conflicting, demand careful and open-minded investigation by people interested and competent in the field of thyroidology. Identification of the thyroid hormones and their metabolites in patients with neoplastic diseases may present us with clues and even more beckoning frontiers for studying the mechanisms by which the thyroid influences growth and maturation.

Finally, I predict that if we encourage and support well trained students of medicine and its basic sciences, who are endowed with the qualities of open-mindedness, imagination and serendipity, the horizons of the thyroidologists will be broadened to extents never previously imagined. Our colleagues in the basic sciences who possess these qualities need only to follow each experiment to its next and logical step. If we clinicians, who have daily opportunities to observe Nature's experiments, demonstrate these qualities, our patients with diseases of the thyroid may lead us into exciting new fields of clinical investigation not previously thought to be related to the thyroid.

The new tools now available and our present basic knowledge of thyroid physiology and metabolism provide us with unlimited opportunities for both basic and applied research in thyroidology. With these new opportunities we as members of the American Goiter Association have obligations to our professional colleagues, our students and the public, to support and continue the type of research into problems of the thyroid which have been described before this meeting and other recent meetings of our Association.

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SOME NEW OBSERVATIONS ON SUBACUTE THYROIDITIS*

PENN G. SKILLERN, M.D., HAROLD E. NELSON, M.D.† AND GEORGE CRILE, JR., M.D.

The Departments of Endocrinology and General Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio

INTRODUCTION

SUBACUTE (granulomatous, acute) nonsuppurative thyroiditis has been generally accepted as being a true inflammation of the thyroid gland since it was first described by de Quervain in 1904 (1). Its course may vary from an acute systemic inflammatory reaction to a smoldering low-grade one (2). The clinical diagnosis of the acute form is usually not difficult for the physician who is familiar with the disease. However, recently we have observed some atypical features which either complicated the clinical diagnosis or resulted in a failure to make the correct clinical diagnosis. The purpose of this paper is to describe these atypical clinical features; to present findings obtained with thyroid-stimulating hormone (TSH) tests, electrophoretic protein pattern determinations and serum colloidal gold tests in both typical and atypical subacute thyroiditis; and to present results with the use of prednisone as a therapeutic agent.

MATERIALS AND METHODS

The clinical records of 66 patients with subacute thyroiditis were reviewed with special reference to the red blood cell count, hemoglobin concentration, and cell volume. Hemoglobin values were measured by a photoelectric colorimeter. Representative case histories of patients with atypical features of subacute thyroiditis will be described. In 3 patients the diagnosis was confirmed by needle biopsy of the thyroid, using the method described by Crile and Vickery (3). The stained microscopic sections of each biopsy specimen were reviewed and considered diagnostic of subacute (granulomatous) thyroiditis by Dr. J. B. Hazard of the Department of Pathology.

Thyroid-stimulating hormone (TSH) tests were performed on 12 patients, using 4 units of thyrotropin according to the method of Jefferies and associates (4) with minor modifications. A tracer dose of approximately 15 to 30 microcuries of radioiodine[1] in cap-

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† Fellow in the Division of Medicine, Cleveland Clinic.

[1] The radioactive material used in this study was supplied by Abbott Laboratories on authorization of the Isotopes Division, Atomic Energy Commission, Oak Ridge, Tennessee.

sule or liquid form was given before and after the administration of TSH. (When the I^{131} was administered, each patient was either fasting or had not eaten for three hours.) Measurements of I^{131} uptake were made directly over the thyroid gland by a scintillation counter. In 10 patients six-hour uptakes, and in 2 patients 24-hour uptakes were determined. Control six-hour TSH tests, using 4 units of TSH, were carried out on 12 euthyroid patients.

Basal metabolic rates were performed in duplicate and the results were averaged. Fractional electrophoretic studies of the serum proteins were made in 6 patients, using Longsworth's modification of the Tiselius procedure (5). The serum colloidal gold test was a slight modification of the method of Maclagan (6), differing by the substitution of commercially prepared colloidal gold solution, with the quantities of serum and barbital buffer constituting the dilution. The pH of the commercial colloidal gold solution was adjusted according to the method of Reich, using known normal and abnormal sera (7, 8).

RESULTS

Clinical Features

Anemia

A significant degree of anemia was observed in 11 (16.7 per cent) of 66 patients with subacute thyroiditis (Table 1). Eight women had hemoglobin levels of less than 11 Gm. per 100 ml. and 3 men had levels less than 12 Gm. per 100 ml. The lowest value observed was 8.3 Gm. per 100 ml. in a woman. The anemia was essentially of the normochromic normocytic type, although slight hypochromasia of the red cells was seen in the blood smears of a few of the patients. The duration of the thyroiditis in 11 pa-

TABLE 1. HEMOGLOBIN VALUES IN 66 PATIENTS WITH SUBACUTE THYROIDITIS. A SIGNIFICANT DEGREE OF ANEMIA WAS PRESENT IN 11 (16.7 PER CENT) OF THE PATIENTS (8 WOMEN AND 3 MEN)

Hemoglobin (Gm. per 100 ml.)	No. of men	No. of women
14–15	0	2
13–13.9	6	13
12–12.9	5	15
11–11.9	1	14
10–10.9	2	3
9– 9.9	0	4
8– 8.9	0	1

tients prior to admission ranged from two to sixteen weeks, with an average of 5.5 weeks. Five had been ill for three weeks, and hemoglobin levels in these patients ranged from 8.3 to 10.8 Gm. per 100 ml. The occurrence of anemia did not seem to be related to the severity of the subacute thyroiditis, nor was there any clinical evidence of significant hemolytic anemia. In all 4 of the 11 patients on whom follow-up hematologic studies were obtained the anemia spontaneously cleared after the thyroiditis had subsided (Table 2).

TABLE 2. HEMOGLOBIN CONTENT, RED BLOOD CELL COUNT AND CELL VOLUME IN 4 PATIENTS WITH SUBACUTE THYROIDITIS, SHOWING SPONTANEOUS RETURN OF VALUES TO THE NORMAL LEVEL AFTER RECOVERY FROM THE THYROIDITIS

Patient No.	Hemoglobin (Gm. per 100 ml.)		Cell volume (ml. per 100 ml.)		Red blood cell count (cells per cu. mm.)	
	Active disease	Recovery	Active disease	Recovery	Active disease	Recovery
1	9.2	13.0	34	42	3,800,000	4,600,000
2	9.0, 9.6	13.5	33, 35	—	3,700,000	—
3	9.6	14.6	32	46	4,300,000	5,300,000
4	8.3	12.4	32	42	3,200,000	4,700,000

The occurrence of a significant degree of anemia in 3 patients with otherwise typical subacute thyroiditis is illustrated by the following case presentations:

Case 1. A 42-year-old woman was first examined here in October 1953. Two weeks previously she had noted pain in the right lobe of the thyroid extending into the neck and to the right ear; this was accompanied by a fever of 102° F. and nervousness. There was definite tenderness over the slightly enlarged right lobe of the thyroid. The red blood cell count was 3,800,000 per cu. mm., hemoglobin content 9.2 Gm. per 100 ml., and cell volume 34 ml. per 100 ml. Examination of the peripheral blood smear revealed a slight degree of anisocytosis, pallor and poikilocytosis. The reticulocyte count was 3.3 per cent; the icterus index 4. The blood urea level was normal, and findings of complete gastrointestinal roentgen studies were normal. Treatment with cortisone resulted in complete relief of symptoms and signs. In April 1954, the red blood cell count was 4,600,000 per cu. mm., hemoglobin content 13 Gm. per 100 ml., and cell volume 42 ml. per 100 ml.

Case 2. A 59-year-old woman was first examined here in April 1953. Four days after extraction of teeth, six weeks previously, she had noted pain in the right lobe of the thyroid, which spread to the left lobe three weeks later. The pain extended to the ears and was aggravated by swallowing. The patient also experienced chills, fever, weakness, and anorexia and had lost 20 pounds in weight. Physical examination revealed a firm, diffuse, tender goiter. Results of laboratory studies were as follows: basal metabolic rate, −16 per cent; hemoglobin values, 9.0 and 9.6 Gm. per 100 ml.; red blood cell counts, 3,680,000 and 3,690,000 per cu. mm., respectively; cell volumes, 33 and 35 ml. per 100 ml.; reticu-

locyte count, 4 per cent; and the icterus index, 4. Examination of a specimen obtained by sternal puncture showed a hypocellular marrow. The blood urea level was normal. An entire series of roentgen studies showed the gastro-intestinal tract to be normal. Treatment with cortisone resulted in complete relief of symptoms and signs of the disease. In November 1954, the hemoglobin content was 13.5 Gm. per 100 ml.

Case 3. A 66-year-old man was first examined here in June 1953. Following an upper respiratory infection, the patient had noted the onset of fever to 102° F., night sweats, hoarseness, weakness and malaise, anorexia, and pain in the thyroid gland extending into the neck. The pain lasted only a few days early in the illness. He also had lost 10 pounds in weight. On physical examination he appeared to be sick. The thyroid gland was firm, slightly tender, and diffusely enlarged. The hemoglobin content of the blood was 9.6 Gm. per 100 ml., the red blood cell count 4,300,000 per cu. mm., and cell volume 32 ml. per 100 ml. The peripheral blood smear showed slight hypochromasia, anisocytosis, poikilocytosis and anisochromia. The sedimentation rate was 1.35 mm. per minute, icterus index 5, and the reticulocyte count 1.6 per cent. The basal metabolic rate was +11 per cent. A needle biopsy revealed the typical histologic picture of subacute (granulomatous) thyroiditis with much fibrous replacement of epithelial cells, neutrophils, lymphocytes and foreign-body giant cells. No treatment was prescribed because the patient had no pain and was feeling better. In September 1953, the hemoglobin content was 14.6 Gm. per 100 ml., red blood cell count 5,300,000 per cu. mm., and cell volume 46 ml. per 100 ml.

Asymptomatic goiter and minimal febrile symptoms

The occurrence of asymptomatic thyroid enlargement with minimal febrile symptoms in subacute thyroiditis is exemplified by the following case summary:

Case 4. A 35-year-old woman was first examined here in August 1955, with a three-month history of rapid pulse, fatigue, goiter, and weight loss of 20 pounds despite a good appetite. The patient said she had had no chills, fever, night sweats, or discomfort in the thyroid area during the illness. Her physician referred the patient here because of differences of opinion as to whether she had Graves' disease. Early in her illness the basal metabolic rate was +14 per cent, serum cholesterol level 190 mg. per 100 ml., and serum protein-bound iodine level 14 micrograms per 100 ml. On physical examination she appeared well. The pulse rate was 84 per minute; oral temperature 98.4 degrees F. There was a nontender, firm, diffuse enlargement of the thyroid, estimated to weigh 50 Gm. Laboratory studies showed a normal red blood cell count and hemoglobin content. The plasma cholesterol level was 130 mg. per 100 ml. The basal metabolic rate was −16 per cent. The 6-hour I^{131} uptakes were 13 per cent before and 12 per cent after 4 units of thyrotropin. Results of a serum colloidal gold test were negative. The prebiopsy diagnosis was probable struma lymphomatosa. A needle biopsy showed subacute (granulomatous) thyroiditis with small follicles separated by fibrous tissue, collections of histiocytes, neutrophils, lymphocytes and giant cells of foreign-body type. No treatment was required. The goiter disappeared three months later.

Anemia, asymptomatic goiter and minimal febrile symptoms

When all of these atypical features are present in the same patient, it may be extremely difficult to establish the clinical diagnosis of subacute thyroiditis, as illustrated by the following case summary:

Case 5. A 50-year-old woman was first examined here on June 8, 1955. Three weeks prior to admission the patient had noted a goiter, but denied any history of discomfort or pain in the neck, chills or night sweats. She had always been nervous but had been much more nervous recently. Anorexia, weight loss of 15 pounds, headache and fatigue had been noted. She had experienced a flare-up of diabetes mellitus with hyperglycemia and glycosuria. The diabetes had been present for twelve years. Physical examination revealed a temperature of 99.4° F. and a pulse rate of 104 per minute. The thyroid gland was diffusely and moderately enlarged (estimated weight, 65 Gm.), very firm, and not tender. Laboratory examination revealed a red blood cell count of 3,200,000 per cu. mm., cell volume of 32 ml. per 100 ml., and hemoglobin content of 8.3 Gm. per 100 ml. The peripheral blood smear showed mild hypochromasia and slight anisocytosis. The Tiselius protein pattern and results of the serum colloidal gold test were normal. The basal metabolic rate was +12 per cent and the serum cholesterol level was 136 mg. per 100 ml. The thyroidal I^{131} uptake was 9 per cent before, and 7 per cent after administration of 4 units of thyrotropin. The findings of an upper gastro-intestinal roentgen study were normal. A diagnosis of subacute thyroiditis was not considered by two clinicians experienced in the diagnosis of thyroid disease, but it was believed that she might have struma lymphomatosa and an associated disease. A needle biopsy revealed the typical microscopic findings of subacute (granulomatous) thyroiditis—extensive fibrosis obliterating the follicles; and the presence of plasma cells, histiocytes, lymphocytes, neutrophils and an occasional giant cell. No treatment was given because the patient began to feel much better while under observation, and her insulin requirement decreased. On her return two months later her symptoms and goiter had disappeared. The blood hemoglobin content was 12.4 Gm. per 100 ml., red blood cell count 4,700,000 per cu. mm. and cell volume 42 ml. per 100 ml. The basal metabolic rate was −26 per cent. The thyroidal I^{131} uptake was 15 per cent. The patient was clinically euthyroid.

Thyroid-Stimulating Hormone (TSH) Tests

The results of the TSH tests, performed on 12 patients with subacute thyroiditis and 12 euthyroid controls are recorded in Table 3. In all but 2 patients with subacute thyroiditis the response to 4 units of TSH was negligible (*i.e.*, less than 100 per cent of an original thyroidal uptake that was 10 per cent or less; and less than 50 per cent of an original uptake that varied from 11 to 50 per cent). In 9 of the 11 patients with subacute thyroiditis, the basal metabolic rates were normal or slightly elevated (Table 3). In the other 2 patients (Table 3) the basal metabolic rates were −16 per cent and −17 per cent late in the course of the disease, which may have been either their normal rates or indicative of a temporary decrease in the production of thyroxine. In 1 of these patients who had positive results with the TSH test and a basal metabolic rate of −16 per cent, the BMR had been +10 per cent six weeks previously. In another patient having positive results with the TSH test and a basal metabolic rate of +12 per cent early in the course of her disease, the basal metabolic rate was −26 per cent two months later. A significant increase in thyroidal I^{131} uptake was induced by 4 units of TSH in all 12 normal euthyroid patients.

TABLE 3. RESULTS OF TSH TESTS (AND BASAL METABOLIC RATES) IN 12 PATIENTS WITH SUBACUTE THYROIDITIS COMPARED WITH NORMAL RESULTS OF TSH TESTS IN 12 NORMAL EUTHYROID PATIENTS

(Results of the TSH test were abnormal in 10 of the 12 cases of subacute thyroiditis)

Acute thyroiditis					Euthyroid controls		
Patient No.	Thyroidal I^{131} uptake		BMR (%)	Duration of disease before det. of I^{131} uptake (wks.)	Control No.	Thyroidal I^{131} uptake	
	Before TSH (%)	After TSH (%)				Before TSH (%)	After TSH (%)
1	10	13	−17	8	1	32	73
2	11	13	− 9	16	2	32	57
3	9	7	+12	3	3	12	24
4	12	16	− 7	6	4	13	33
5	13	12	−16	8	5	12	39
6	10	8	− 7	6	6	17	55
7	6	10	+ 1	8	7	18	57
8	9	10	—	2	8	11	38
9	7	9	+16	3	9	12	30
10	9	10	+19	4	10	22	55
11	12	19	− 5	3	11	19	41
12	6	13	+ 4	8	12	16	50

Electrophoretic Protein Studies

Electrophoretic analyses of plasma proteins were performed on 6 patients (Table 4). The patterns were essentially normal except for a moderate decrease in serum albumin in 5, a slight increase in gamma globulin in 2, an increase in alpha 1 and 2 globulins in 1, and a slight elevation of beta globulin in 1.

Serum Colloidal Gold Tests

Serum colloidal gold tests were performed on 11 patients. The results were normal in 9 of the 11 patients. Six of these values are listed with the respective electrophoretic patterns in Table 4.

Treatment with Prednisone

Six patients were treated with prednisone. One tablet (5 mg.) was given four times a day for the first week until all the symptoms were controlled. Then the dosage was reduced to 1 tablet three times a day for a week, and then to 1 tablet twice a day for the next two weeks. The drug was then

TABLE 4. TISELIUS ELECTROPHORETIC PROTEIN PATTERNS AND SERUM COLLOIDAL GOLD CURVES IN 6 PATIENTS WITH SUBACUTE THYROIDITIS, SHOWING A MODERATE DECREASE IN ALBUMIN IN MOST PATIENTS BUT LITTLE CONSISTENT CHANGE IN GLOBULINS

Patient No.	Albumin (Gm. per 100 ml.) (3.72–5.11)*	Globulin (Gm. per 100 ml.) Alpha [α1—.43±.10]* [α2—.62±.12]	Beta (.65–1.07)*	Gamma (.60–.91)*	Colloidal gold (000000–551000)*
1	3.77	α2 0.43	0.93	0.94	110000
2	3.23	α2 0.59	0.85	0.91	211000
3	3.23	α2 0.54	1.06	0.99	000000
4	3.30	α2 0.62	1.01	0.80	000000
5	2.50	α2 0.52	0.97	0.69	000000
6	3.22	α1 0.71 α2 1.04	1.25	0.83	000000

* Normal values.

stopped. If the disease flared up, the treatment was continued for another month. A dose of 5 mg. twice a day seemed sufficient to control the symptoms of the disease in most patients.

In all patients the symptoms were largely ameliorated in less than forty-eight hours after treatment was begun. In 2 of the patients the symptoms of the disease recurred after one month and the therapy was restarted; one of them was symptom-free after another month; the other required four months of treatment before the symptoms subsided. Edema did not occur in any of the patients, even though salt restriction was not prescribed.

DISCUSSION

The typical clinical features of subacute thyroiditis are subjective and objective pain in the thyroid gland often extending up into the neck and ears, enlargement of the thyroid, fever, chills, sweating, malaise, weakness, anorexia, weight loss, and in some instances, equivocal hyperthyroidism.

The occurrence of a significant normochromic normocytic (occasionally slightly hypochromic) anemia in 11 (16.7 per cent) of 66 patients with subacute thyroiditis complicated the diagnosis of the typical cases and helped to obscure the clinical diagnosis in 1 patient with atypical subacute thyroiditis until a needle biopsy was performed. Frequently the presence of hemoglobin values as low as 8 to 10 Gm. per 100 ml. resulted in a fruitless search for other causes of the anemia; gastro-intestinal roentgen studies and additional blood studies were made, because it was not appreciated that the anemia could be due to the effects of the subacute thyroiditis it-

self. The pathologic-physiologic mechanisms for the anemia due to subacute thyroiditis are as yet unknown, but we believe that they are probably the same as those observed in other infections. The exact nature of these mechanisms is still obscure, but it is believed that there may be depression of the bone marrow and interference with iron metabolism (9).

The absence of any subjective or objective discomfort in the goiters and the lack of significant febrile symptoms or signs in 2 of our patients with subacute thyroiditis led two clinicians, experienced in the diagnosis of thyroid disease, to make an incorrect clinical diagnosis in each instance. The occurrence of a hemoglobin value of 8.3 Gm. per 100 ml. in 1 of these patients made the diagnosis even more difficult. It was believed that both patients probably had struma lymphomatosa until the diagnosis of subacute thyroiditis was proved by the results of needle biopsy of the thyroid glands. Crile and Rumsey (2) and Werner (10) have previously pointed out that mild subjective symptoms such as tightness in the neck, choking sensation and progressive swelling may occur in some patients with subacute thyroiditis, and that tenderness and enlargement may be so minimal as to be misleading. Such subjective symptoms are frequently seen in anxiety tension states and in other conditions causing thyroid enlargement, especially struma lymphomatosa, nontoxic adenomatous goiter, or even carcinoma. The differential diagnosis in our 2 cases was additionally complicated by the failure to elicit by direct questioning any history of subjective discomfort or to find any objective tenderness by palpation of the thyroid.

Certain characteristic laboratory findings are well known as aids in the diagnosis of this disease. The sedimentation rate usually is elevated, but its value is limited by its nonspecificity. The basal metabolic rate and protein-bound iodine content of the serum usually are normal or elevated (2, 11, 12), but the occurrence of a low thyroidal radioiodine uptake is much more useful as a diagnostic aid (2, 11–15). Other than administration of iodine or desiccated thyroid to patients with goiter, we and others (13, 15) have observed that another cause of low uptake of I^{131} associated with diffuse goiter may be struma lymphomatosa. Four of the 32 patients with struma lymphomatosa in our series had low I^{131} uptakes; 3 of these 4 had clinical evidence of hypothyroidism. We have observed that in struma lymphomatosa the basal metabolic rate is low if the I^{131} uptake is low, whereas in subacute thyroiditis the basal metabolic rate usually is normal or slightly elevated early in the course of the disease, although this may not be true in the later phases.

In 10 of our 12 patients with subacute thyroiditis, the administration of thyrotropin did not cause a significant increase in the I^{131} uptake. On the other hand, Robbins and associates (12) reported that the administration

of thyrotropin usually causes a significant increase in I^{131} uptake. This difference can be explained by the fact that these investigators gave larger doses of TSH over a longer period of time than we did; the significant increases which they obtained indicate that the thyroid cells were only partially damaged and capable of responding to maximal TSH stimulation. Previous observations, as well as our own, indicate that a dose of 4 units of TSH is sufficient to increase the thyroidal I^{131} uptake significantly in patients with normal thyroid function (4, 16–18). Both the low or low-normal radioiodine uptake and failure to respond to a small dose of TSH in subacute thyroiditis corroborate the observations of others that the iodine-trapping function of the thyroid cells usually is temporarily impaired by the inflammatory disease (2, 12) instead of being depressed by an increase in circulating thyroxine. We believe that this failure to respond to a small dose of TSH may be an additional aid in the diagnosis of atypical subacute thyroiditis. Although almost all patients with struma lymphomatosa have abnormal findings with TSH tests, the initial 6-hour or 24-hour thyroidal I^{131} uptakes frequently are normal or high (19). Patients with nontoxic adenomatous goiter or thyroid carcinoma usually can be differentiated from those having subacute thyroiditis on the basis of clinical findings and also by the occurrence of a normal I^{131} uptake which is significantly increased by TSH (18, 19).

Fromm and associates (20) reported a decrease in serum albumin and a significant increase in alpha, beta and gamma globulin levels in 1 patient with subacute thyroiditis, and Werner (10) reported a decrease in albumin and an increase in alpha and gamma globulin levels in 1 such patient. The nonspecific changes in the electrophoretic protein patterns are of little diagnostic help, especially in differentiating patients with struma lymphomatosa, who usually have a higher gamma globulin level and often an elevation of the beta globulin level (19). The occurrence of negative results with the colloidal gold test in almost all patients with subacute thyroiditis may be of some help, since most patients with struma lymphomatosa have positive results with this test, due to higher gamma globulin levels (7, 19).

One disadvantage of the use of cortisone or hydrocortisone in the treatment of subacute thyroiditis is the occurrence of edema in some patients unless a low-salt diet is given. This did not occur in our 6 patients treated with prednisone, because this drug has much less effect on electrolytes than does cortisone or hydrocortisone. Furthermore, prednisone seemed to be as effective as cortisone in suppressing symptoms and signs until the self-limited disease subsided. If the patient has a history of duodenal ulcer or diabetes mellitus, we believe that roentgen therapy should be used instead of prednisone or cortisone, because of the danger of precipitating gastro-intestinal hemorrhage or a flare-up of the diabetes.

SUMMARY

1. A significant normochromic normocytic anemia was observed in 11 (16.7 per cent) of 66 patients with subacute thyroiditis.

2. The diagnosis of subacute thyroiditis may be obscured by asymptomatic goiter, the occurrence of minimal or no febrile symptoms (as observed in 2 patients in whom the diagnosis was proved by the results of needle biopsy), and the concurrence of anemia (as also observed in 1 of the 2 patients with few or no febrile symptoms).

3. Four units of TSH failed to increase the low or low-normal thyroidal I^{131} uptake significantly in 10 of 12 patients with subacute thyroiditis, in contrast to the significant increase noted in control euthyroid patients.

4. Determination of electrophoretic protein patterns showed a moderate decrease in albumin in 5 of 6 patients, a slight increase in gamma globulin in 2 of 6 patients, and an increase in alpha and beta globulins in 1 patient with subacute thyroiditis.

5. Prednisone is as effective as cortisone in controlling the symptoms and signs of subacute thyroiditis and has the advantage of not causing edema.

Addendum

Since this paper was submitted for publication, Stemmermann has reported that the alpha-2 globulin fraction was elevated in 4 patients with subacute thyroiditis, as determined by paper electrophoresis. (Stemmermann, G. N.: Serum protein changes in subacute thyroiditis, *J.A.M.A.* **162**: 31 (Sept. 1) 1956.)

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CLINICO-PATHOLOGIC STUDY OF 261 SURGICAL CASES OF SO-CALLED "THYROIDITIS"*

W. ARTHUR HARLAND, M.B., B.Ch.† AND VIRGINIA KNEELAND FRANTZ, M.D.

The Laboratories of Surgical Pathology of the College of Physicians and Surgeons, Columbia University and of the Presbyterian Hospital, New York, N. Y.

IN THIS study, 261 cases in which the diagnosis of thyroiditis was made were reviewed with regard to their clinical and pathologic features. This represented an incidence of 3.5 per cent of all thyroid operations (7,448) at the Presbyterian Hospital in New York over a 34-year period. These cases were distributed as shown in Table 1.

Acute infectious or suppurative thyroiditis is rare and results from bacterial invasion of the thyroid from another septic focus in the body, usually by way of the blood stream. Pneumococci were isolated directly from the thyroid in 1 of our 2 cases, and this is said to be the most common causative agent (1). The disease is frequently associated with pre-existing goiter. *Chronic specific thyroiditis* is even more rare. In this series there was 1 case of syphilitic gumma of the thyroid and this responded well to chemotherapy. All cases that had been diagnosed as tuberculosis of the thyroid were reclassified as granulomatous thyroiditis and there were no cases of fungus infection or of parasitic invasion of the thyroid.

Radiation thyroiditis results from either external or internal radiation. It is not a clinical entity and the signs and symptoms are those of the underlying disease. All 7 cases in this series had undergone external radiation, 5 for hyperthyroidism and 2 for carcinoma. In each case there was an excessive amount of scar tissue in the gland and in 1 there was still active inflammation three years after the last dose of radiation. The only constant finding was the presence of large hyperchromatic nuclei. In addition there were variable degrees of disorganization and the colloid was sometimes vacuolated. Only in 1 case was there organized lymphoid tissue, but the epithelial changes bore no resemblance to those of lymphoid struma.

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† Present address: St. Joseph's Hospital, Chatham, Ontario, Canada.

TABLE 1. INCIDENCE OF "THYROIDITIS" IN 7,448 THYROID OPERATIONS
(Presbyterian Hospital, New York, 1919–1953)

	No. of cases		Incidence (%)	
I. KNOWN ETIOLOGY				
A. Infectious				
1. Acute	2		0.03	
2. Chronic	1		0.01	
B. Traumatic	0			
C. Due to physical or chemical agents				
1. Radiation	7		0.09	
2. Chemical	0			
II. UNKNOWN ETIOLOGY				
A. Granulomatous (deQuervain)	27		0.36	
B. Invasive fibrous (Riedel)	8		0.11	
C. Lymphocytic			2.91	
1. *Struma lymphomatosa*				
a) With diffuse oxyphilia (Hashimoto)	70	116	0.94	1.6
b) With little or no oxyphilia	46		0.62	
2. Associated with other thyroid disorders				
a) Nontoxic nodular goiter	43		0.58	
b) Diffuse and nodular toxic goiter	38		0.51	
c) Carcinoma		100		
1) Primary	17		0.23	
2) Metastatic	0			
d) Lymphosarcoma	2		0.03	
	261		*3.5*	

Granulomatous thyroiditis. There were 27 cases in our series. The ratio of female to male was more than 5 to 1 and the great majority of cases occurred in the fourth and fifth decades. The symptomatology was varied; less than half the patients complained of pain in the thyroid, and fever usually was mild or absent. General malaise and weight loss were the most common symptoms. The duration of the disease was variable; 1 patient had symptoms for two years prior to surgery. The positive laboratory findings included elevations of the erythrocyte sedimentation and basal metabolic rates and a depressed thyroidal uptake of radioactive iodine. The operative findings were variable, but 2 patients had edema of the cervical muscles and 10 had loose adhesions to the surrounding muscles and to the trachea. The characteristic lesion microscopically was the granuloma composed of a central mass of colloid with a margin of giant cells and mononuclear cells. Less commonly, polymorphoneclear leuko-

cytes were seen. The giant cells and mononuclear cells were often noted to have ingested colloid particles. In addition there was usually a moderate degree of fibrosis and, more rarely, fibroblastic activity both in the gland and in the gland capsule. No chronologic sequence could be traced to show a relationship between the duration of symptoms and the type of lesion.

Clinicially, the diagnostic feature of the disease, apart from the history and physical findings, is the paradoxical association of a depressed thyroidal uptake of radioactive iodine with an elevated level of serum protein-bound iodine (2). The prognosis of the disease is good. In only 1 of our patients did mild hypothyroidism develop after a subtotal thyroidectomy. The cause of the disease is not known and the treatment is empirical. Only a minority of the patients have to be operated on, and the majority respond well to either radiation or cortisone therapy.

Invasive fibrous thyroiditis or Riedel's struma was observed in 8 patients, with a ratio of 3 females to 1 male. The majority of the cases occurred in the third to the fifth decades. Pre-existing goiter was noted in 3 patients. Symptoms were minimal, except in 1 man in whom severe symptoms of tracheal compression developed. The erythrocyte sedimentation rate was usually elevated. In the only case in which it was estimated, the thyroidal uptake of radioactive iodine was depressed.

Operation was usually difficult because of dense fibrous adhesions binding the gland to the surrounding tissues. Microscopic examination showed dense hyaline fibrous tissue and a chronic inflammatory-cell infiltrate. There was no resemblance between this picture and that of struma lymphomatosa but the similarity of the clinical, operative and pathologic findings suggest a possible relationship to granulomatous thyroiditis.

Struma lymphomatosa is defined as a disease of the thyroid characterized by a diffuse and focal infiltration of cells of the lymphoid series throughout both lobes of the thyroid gland, with germinal centers in the confluent zones, an associated epithelial abnormality and fibrosis. On the basis of morphologic differences in the epithelium of the thyroid, two main groups were distinguished among our 116 cases.

In the first of these (70 cases) there was a diffuse oxyphilic change in the epithelium, with small round follicles and little or no colloid. Collections of mononuclear cells were often present within the follicles and there was great variation in the degree of fibrosis. The latter sometimes gave rise to a lobulated appearance in the gland simulating nodules clinically. This picture was first described by Hashimoto (3). It is a disease that is rare in the male and in the Negro, and occurs predominantly in the fourth and fifth decades. Symptoms are few but there is a definite tendency to hypothyroidism. The laboratory findings are usually of little value in

diagnosis, although there is the interesting association of achlorhydria in many cases (4, 5).

The second main group (46 cases) had epithelial cells that were smaller and more active in appearance. They were arranged in small, usually empty follicles that had a star-shaped outline. Once again mononuclear cells appeared within the follicles. An additional feature was the collection of epithelial cells in clumps at points of dense lymphoid infiltration, suggestive of squamous metaplasia. Patients with this condition had a wider age distribution than those in the first group (the majority being in the second and third decades), and males were rarely affected. There were few clinical signs apart from diffuse firm enlargement of the thyroid, although there seemed to be a greater tendency to hypothyroidism in this group. The laboratory findings are usually normal, although high levels of serum protein-bound iodine in association with low levels of butanol-extractable iodine have been observed (6). There are some reports suggesting that this type of struma lymphomatosa responds to thyroid therapy.

In an attempt to establish a relationship between struma lymphomatosa and various other diseases of the thyroid in which lymphocytic infiltrations occur, 100 cases were examined which had as a common feature infiltrations of lymphocytes and related epithelial changes resembling those seen in the diffuse disease. Special attention was given to those patients who had undergone surgical procedures on two occasions, in the hope of tracing a change from focal to diffuse involvement. In no case was such a relationship obvious. The diseases studied included nontoxic nodular goiter, toxic diffuse and toxic nodular goiter, carcinoma of the thyroid and lymphosarcoma of the thyroid. Lymphocytic infiltrations were most marked in association with toxic goiter, but in no case was the typical picture of struma lymphomatosa seen.

SUMMARY AND CONCLUSIONS

A few points in this study:

1. Among the patients with granulomatous thyroiditis undergoing operation, more than half did not have the typical picture of subacute thyroiditis, namely migrating pain and tenderness in the thyroid.

2. Riedel's struma is a very rare disease and its chief characteristic is the invasive fibrosis that surrounds and obliterates the thyroid. The pathologist, therefore, must be given an operative report before reaching this diagnosis.

3. Operative and clinical reports are essential in assessing struma lymphomatosa. The whole gland is involved, and there are no capsular adhesions. There are two histologic types, distinguished by the epithelial changes.

The first of these occurs in older women, and the second in adolescents and younger adults.

4. Fibrosis was described by Hashimoto (3) as one of the features of the disease bearing his name. This fibrosis can be marked at times, but it does not extend beyond the gland capsule, and thus differs from invasive fibrous thyroiditis.

5. There was no evidence to suggest a relationship between struma lymphomatosa and other diseases of the thyroid in which lymphocyte infiltrations occur. It is suggested that the term "Hashimoto's disease" be restricted to those cases in which both lobes of the thyroid are involved diffusely.

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THE SIGNIFICANCE OF LOW THYROID RESERVE*†

W. McK. JEFFERIES, M.D., L. W. KELLY, JR., M.D.,‡
R. P. LEVY, M.D.,§ G. W. COOPER, M.D.‖ AND
R. L. PROUTY, M.D.

The Department of Medicine, Western Reserve University School of Medicine, and University Hospitals, Cleveland, Ohio

IN A previous report from this clinic (1) the value of a test utilizing the effect of a single intramuscular injection of thyroid-stimulating hormone (TSH) in the diagnosis of obscure hypothyroidism was presented. Of 37 patients tested because of suspected hypothyroidism, 3 were found to manifest a condition that had not previously been clearly recognized, and which was termed "low thyroid reserve." It was characterized by a normal three-hour thyroidal uptake of I^{131} and serum protein-bound iodine (PBI) level, but a failure of either to respond to stimulation with TSH. It was attributed to the presence of a remnant of thyroid tissue which was being stimulated maximally by endogenous TSH and hence could not respond further to the exogenous hormone administered in the test. Additional experiences with this condition were published in a subsequent brief report (2). It was also observed that in some circumstances I^{131} uptake would rise following administration of TSH but the serum PBI level would not, and in others I^{131} uptake would not rise but the PBI level would (3). Martin and Stanbury (4), in a study of the response of the I^{131}-treated thyroid to TSH, also observed patients with normal thyroidal I^{131} uptakes and serum PBI levels which failed to respond to stimulation. In view of the theoretical interest in this phenomenon as a sequel to sub-

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‡ Former Zakrschefska Fellow in Medicine. Present address: The Nalle Clinic, Charlotte 2, North Carolina.

§ Hoover Fellow in Medicine.

‖ Former Melbourne Fellow. Present address: London House, Guilford St., W.C. 1, London, England.

total thyroidectomy or I^{131} therapy, as well as its potential clinical importance, further studies have been made in an attempt to answer some of the questions that arose concerning the diagnosis, nature and prognosis of this disorder.

METHODS

The technic of the TSH test remained essentially the same as that described in the previous report (1), except that since June, 1953 (test #146) a dosage of 5 U.S.P. units of thyrotropin[1] was used instead of the 10-mg. (4 U.S.P. units) dosage employed in the earlier tests (Fig. 1). Tracers of 10 or 15 microcuries were administered to adults, whereas

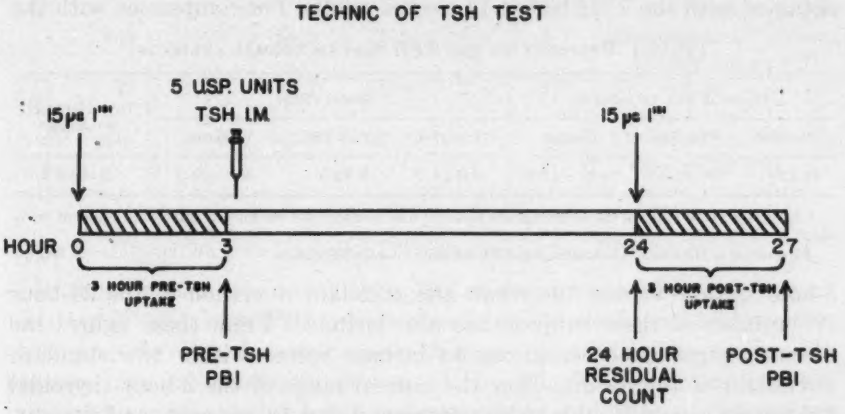

FIG. 1. The technic of the TSH test. Tracer doses of I^{131} are administered orally with the subject fasting. I^{131} uptakes are measured over the thyroid gland. The uptake of the second tracer is determined by correcting for the residual count of the first tracer and its decay over the subsequent three-hour period.

children between the ages of 10 and 17 years received 5 microcuries and children under 10, between 1 and 3 microcuries. The test consists essentially of a comparison of both the 3-hour thyroidal uptake of I^{131} (expressed as a percentage of the administered dose) and the serum PBI level, before and twenty-four hours after a single intramuscular injection of TSH. The 3-hour uptake is preferred to the 24-hour uptake of the tracer because it is a more accurate indication of the *rate* of uptake of iodide by the thyroid gland; but with the shorter period of uptake, tracer doses must be given while the subject is in a fasting state in order to avoid variations in absorption rate. Since the change in serum PBI level reflects release of thyroid hormone, results of this test indicate the effect of the injection of TSH upon both the rate of uptake of iodide and the release of hormone by the gland.

As in the earlier tests, the concentration of serum PBI was assayed by a modification

[1] The thyrotropin (Thytropar) used in this study was generously supplied by the Armour Laboratories. The change of dosage used in the test resulted from a change of dosage supplied in the vials to 10 units instead of the previous 20 mg.

of the method of Barker (5), each sample being run in duplicate. Prolonged experience with this technic has indicated that a change of 1 microgram or greater is probably significant.

RESULTS

Since by definition low thyroid reserve implies the presence of a normal pre-TSH 3-hour thyroidal I^{131} uptake and serum PBI level and a failure of these indices to change significantly following administration of TSH, it was first necessary to determine the normal range of these values as well as the minimum change which could be considered a significant response. In Table 1 are presented the means and standard deviations of the results obtained with the TSH test in 12 normal adults. For comparison with the

TABLE 1. RESPONSE TO THE TSH TEST IN NORMAL SUBJECTS

Thyroidal 3-hr. I^{131} uptake*			Serum PBI†			Thyroidal 24-hr. I^{131} uptake*
Pre-TSH	Post-TSH	Change	Pre-TSH	Post-TSH	Change	
10.1±4.1	30.5±9.6	+20.4±7.8	5.8±1.0	8.9±1.7	+3.1±1.1	29.3±6.3

* Expressed as the mean of the percentage of the tracer dose counted over the thyroid gland with standard deviation.

† Expressed as the mean in micrograms per 100 ml. with standard deviation.

3-hour uptake values, the mean and standard deviation of the 24-hour I^{131} uptakes of these subjects are also included. From these figures the normal ranges were considered to include values within two standard deviations of the means. Thus the normal range of the 3-hour thyroidal I^{131} uptake would include values between 2 and 18 per cent; and the normal range for the serum PBI level would include values between 3.8 and 7.8 micrograms (μg.) per 100 ml. Similarly, the minimum significant rise in 3-hour uptake would be 5 per cent, and in PBI, 1 microgram.

As experience with this test accumulated it became evident that, in addition to the instances in which neither the I^{131} uptake nor the PBI level responded to TSH (Type 1), several other types of response suggested the possibility of low thyroid reserve. These included instances in which I^{131} uptake did not rise but the PBI level did (Type 2); those in which I^{131} uptake rose but the PBI level did not (Type 3); those in which I^{131} uptake was characteristic of low reserve but the PBI level was lower than normal (Type 4); and those in which I^{131} uptake was elevated but the PBI level was characteristic of low reserve (Type 5). Typical examples of these 5 groups are presented in Table 2. Cases were also seen in which both I^{131} uptake and the PBI level were elevated and failed to respond to TSH. These presented no features suggestive of low thyroid reserve, being cases of hyperthyroidism, so they are not included in this discussion. Similarly, cases of frank hypothyroidism, in which both I^{131} uptake and PBI level were low and failed to respond to TSH, are not included.

TABLE 2. TYPES OF TSH TEST RESULTS SUGGESTING LOW RESERVE

Type No.	Test No.	Thyroidal I^{131} uptake (% tracer dose)			Serum PBI (μg./100 ml.)		Classification
		Pre-TSH (3-hr.)	Post-TSH (3-hr.)	24-hr.	Pre-TSH	Post-TSH	
1	190	12.4	12.3	21.6	4.2	4.1	No response in I^{131} uptake or PBI
2	338	17.8	18.5	28.4	6.3	8.4	No response in I^{131} uptake. Response in PBI
3	495	9.0	24.8	21.8	4.6	4.7	Response in I^{131} uptake. No response in PBI
4	92	10.7	12.7	25.6	2.8	3.3	No response in I^{131} uptake. Low PBI
5	345	32.2	43.3	52.3	4.2	4.8	Elevated I^{131} uptake. No response in PBI

Type 1—*No response in thyroidal I^{131} uptake or serum PBI level*

In those instances in which there was no response to TSH with respect to either I^{131} uptake or PBI level, a question to be considered was whether these subjects might for some reason be resistant to TSH. This was readily answered by administering desiccated thyroid. With this therapy the initial 3-hour uptake decreased, consistent with inhibition of endogenous TSH, thereby enabling a response to the exogenous TSH administered in the test to become evident. An example of this sequence of events is presented in Table 3. As yet, no instance of a subject being resistant to TSH

TABLE 3. EFFECT OF ADMINISTRATION OF DESICCATED THYROID ON LOW THYROID RESERVE

(Patient M.C., a 38-year-old female)

Date	Thyroidal I^{131} uptake (% tracer dose)			Serum PBI (μg./100 ml.)	
	Pre-TSH (3-hr)	Post-TSH (3-hr.)	24-hr.	Pre-TSH	Post-TSH
Aug. 1951	Acute nonspecific thyroiditis				
March 1953	8.2	11.5	17.2	6.0	5.8
Nov. 1953	Thyroid begun in dosage of 1 grain daily				
March 1954	2.8	12.3	11.8	5.1	6.8

has been observed in these tests, but it is known that daily injections of this hormone for ten or more days to either experimental animals (6) or human subjects (7) may result in the development of a refractory state.

The question whether a larger dose of TSH than the 5 units administered with the test might elicit a response in these patients was also considered. Dosages as great as 10 units of TSH daily for three days were therefore tried, but no significant response occurred.

The types of cases in which there was no response in either I^{131} uptake or PBI level are listed in Table 4. Of the 20 such cases seen in the first 500 TSH tests performed in this clinic, 6 occurred after I^{131} therapy for

TABLE 4. LOW THYROID RESERVE—TYPE 1: NO RESPONSE IN THYROIDAL I^{131} UPTAKE OR SERUM PBI LEVEL

	No. of cases
After I^{131} therapy for Graves' disease (intervals 5 mos. to 6 yrs.)	6
After subtotal thyroidectomy (intervals 6 mos. to 34 yrs.)	8
for Graves' disease 4	
for toxic nodular goiter 1	
for nontoxic goiter 2	
for goiter of unknown type 1	
After acute nonspecific thyroiditis	2
With subacute nonspecific thyroiditis	2
Three weeks after cessation of prolonged thyroid medication	1
Chronic heart failure with ? myxedema	1
Total	*20*

Graves' disease and 8 after subtotal thyroidectomy for various types of goiter. Two were seen in patients who had had attacks of acute nonspecific thyroiditis seventeen months and five years earlier respectively, and 2 were in patients with subacute nonspecific thyroiditis of two months' and ten months' duration respectively. One occurred in a patient who had received desiccated thyroid, 2 grains daily, for a prolonged period until its withdrawal three weeks prior to the test. Twelve months later the results of the test were normal in this subject. Her thyroid had apparently not yet recovered normal reserve at the time of the first test, which was presumably made while her gland was being stimulated maximally by endogenous TSH. One such result was noted in an elderly man with chronic congestive heart failure whose appearance and symptoms suggested myxedema, but whose plasma cholesterol level was only 93 mg. per 100 ml. Unfortunately no follow-up tests could be performed in this case.

Type 2—*No response in thyroidal I^{131} uptake; normal response in serum PBI level*

The second type of response, in which the I^{131} uptake fails to respond but the PBI level does, suggests that the thyroid's iodide-trapping mechanism is already working at a maximum rate but the mechanism accounting for hormone release is not. This may be an artefact in at least some instances, however. As was pointed out in earlier reports (1, 2) transient exposure to iodide prior to the test may affect the thyroid gland so that, although the

TABLE 5. RESULTS OF TSH TESTS IN SUBJECTS WITH PREVIOUS MILD EXPOSURE TO IODIDE

Test No.	Thyroidal I^{131} uptake (% tracer dose)				Serum PBI (μg./100 ml.)			Remarks
	Pre-TSH (3-hr.)	Post-TSH (3-hr.)	Change	24-hr.	Pre-TSH	Post-TSH	Change	
99	6.0	4.9	−1.1	19.9	5.7	9.8	+4.1	Iodide on skin for lumbar puncture several days before
111	5.7	5.3	−0.4	15.6	4.5	6.6	+2.1	I.V. pyelogram 5 days before
283	8.3	9.5	+1.2	19.9	5.3	7.8	+2.5	Patient 2 yrs. old, receiving cod liver oil
319	9.2	12.7	+3.5	15.2	7.5	12.0	+4.5	Patient 7 mos. old, receiving Percomorphum oil
342	12.5	9.7	−2.8	15.6	4.1	8.1	+4.0	Patient 2 yrs. old, receiving cod liver oil
103	4.9	5.9	+1.0	7.2	11.9	21.2	+9.3	Salpingogram several months before

pre-TSH 3-hour I^{131} uptake is within normal limits, no significant rise follows the administration of TSH. After a suitable interval, usually six weeks or longer, repetition of the TSH test on such patients yields normal results. Although the mechanism of this effect is not known, it is postulated that in these instances the thyroid gland is partially saturated with iodide to such an extent that the 3-hour uptake may remain within normal limits but it cannot increase with TSH stimulation. An alternative explanation would be specific inhibition of the action of TSH on the trapping mechanism without any effect on its action on hormone release. In Table 5 are listed the results of the test in 5 subjects who had previously been exposed to iodide. Three were young children taking vitamin preparations prepared from fish liver oils with high iodide content; 1 had had the skin

painted with tincture of iodine in preparation for a lumbar puncture; and 1 had had an intravenous pyelogram five days before. It is evident that the 24-hour I^{131} uptake tends to be low in these cases, so this may serve as a clue to the iodide exposure. This type of iodide effect is in contrast to the effect of persistent exposure to larger quantities of iodide; in these instances, no significant uptake of I^{131} by the gland occurs either before or after TSH. Also included in Table 5 are the results of a test (No. 103) on a patient who had had a salpingogram several months previously, illustrating how unexpectedly high PBI levels indicate the persistence of

TABLE 6. LOW THYROID RESERVE—TYPE 2: NO RESPONSE IN THYROIDAL I^{131} UPTAKE, BUT NORMAL RESPONSE IN SERUM PBI LEVEL

	No. of cases
Definite iodide exposure	5
Probable iodide exposure	4
After subtotal thyroidectomy for Graves' disease (interval 4 mos. to 5 yrs.)	3
Three to four weeks after cessation of prolonged thyroid medication	2
After suppurative thyroiditis (interval 7 mos.)	1
Nontoxic diffuse goiter	1
Nontoxic multinodular goiter	1
Recovering from acute glomerulo-nephritis	1
Arteriosclerotic heart disease with chronic failure	1
Total	*19*

an abnormal source of organic iodide in the body—in this instance, the iodinated oil which had been injected into the peritoneal cavity.

Of the 19 results of this type observed among the first 500 TSH tests performed in this clinic, 5 were associated with known iodide exposure and 4 with probable iodide exposure. In the remaining 10 there was no history of contact with iodine despite careful questioning of the patient, and 24-hour I^{131} uptakes were well within the normal range. A typical result from this group is the one used as an example of Type 2 response in Table 2 (test No. 338). The subject was a 16-year-old girl with a nontoxic diffuse goiter. Although previous exposure to iodide cannot be definitely ruled out, these findings suggest that a state can be present in which the iodide-trapping mechanism of the thyroid does not respond normally to exogenous TSH, whereas the mechanism for hormonal release does. The conditions in which these results were obtained are listed in Table 6.

Type 3—*Normal response in thyroidal I^{131} uptake; no response in serum PBI level*

The third type of result, in which the I^{131} response is normal but the PBI level fails to rise, suggests that the iodide-trapping mechanism can respond but the hormone release mechanism cannot. It has been found, however, that such a response is usually due to a lack of stored hormone in the thyroid gland. This has been demonstrated in several ways. It was noted that with persons who had been receiving sufficiently large doses of desiccated thyroid (0.1 Gm. daily or more) for several years and who were subsequently found to have normal thyroid glands, TSH tests performed while they were still taking the medication consistently showed a good response in I^{131} uptake but no significant rise in PBI level. Similar patterns of response were observed in cases with hypopituitarism or with functioning adenoma of the thyroid, in which depression of endogenous TSH would be expected. They were also seen in patients who had been receiving antithyroid drugs such as propylthiouracil or methimazole for several months, in whom inhibition of hormone formation would cause depletion of stores. It was therefore postulated that the rise in PBI level which occurs twenty-four hours after an injection of TSH is due chiefly to release of stored hormone rather than to accelerated formation of new hormone.

In order to test this hypothesis further, the following experiment was performed. A normal subject underwent a preliminary TSH test. The results were: pre-TSH 3-hour I^{131} uptake, 11.5 per cent; post-TSH 3-hour I^{131} uptake, 24.7 per cent; 24-hour I^{131} uptake, 26.1 per cent; pre-TSH serum PBI level, 6.4 μg.; and post-TSH PBI level, 9.5 μg. per 100 ml. The subject was given methimazole in a dosage sufficient to block further formation of thyroid hormone. The completeness of the block was verified by the observation that after administration of a tracer of 100 microcuries of I^{131} there was no significant retention of radioactivity in the gland twenty-four hours later and no significant quantity of PBI^{131} appeared in the blood for forty-eight hours. While administration of methimazole was continued, a dose of 5 units of TSH was injected intramuscularly. Twenty-four hours later the serum PBI had risen from a pre-injection level of 6.1 μg. to a level of 9.0 μg. per 100 ml. Since this rise was practically identical with that observed before the methimazole was administered (+3.1 μg. and +2.9 μg., respectively), and since formation of new hormone was blocked during this period, it is evident that the rise in PBI level which occurs within twenty-four hours of an injection of TSH is due almost entirely to release of previously stored hormone rather than to formation of new hormone. A gland which does not contain a significant amount of stored hormone, therefore, would not be expected to contribute to a

significant rise in the serum PBI level within twenty-four hours of an injection of TSH, even though it was capable of normal function.

In order to determine whether the serum PBI concentration might rise later in such a subject, levels were measured at 24-hour intervals for three days following an injection of 5 units of TSH in a patient with potentially normal thyroid function who had been taking 5 grains of desiccated thyroid daily for several years. In Figure 2 her serum PBI curve is compared to that of a normal subject who had not been taking thyroid medication. Although the differences between the values on successive days in the

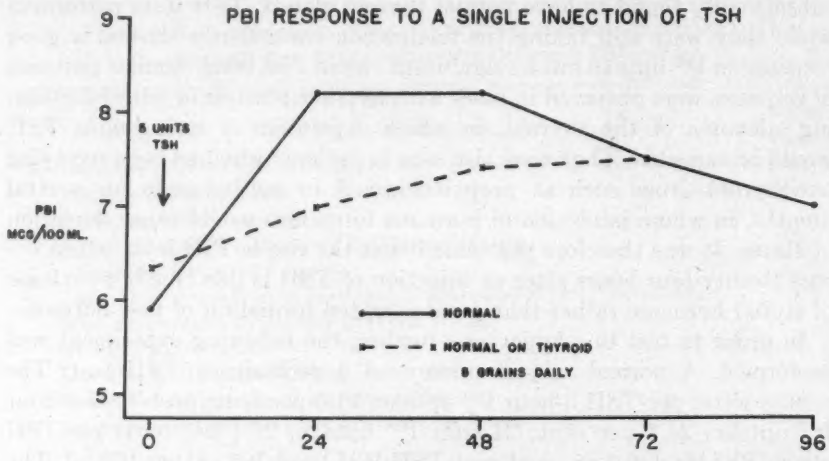

FIG. 2. A comparison of the serum PBI response to a single intramuscular injection of 5 U.S.P. units of TSH in a normal subject without treatment and in a normal subject who had been receiving 5 grains of U.S.P. desiccated thyroid daily for several years.

patient taking thyroid are not significant, the consistency of the curve suggests that a slight rise occurred up to the third day. The difference in contour of this curve from that of the normal subject without thyroid, in whom the peak level was reached in twenty-four hours, suggests that this rise was due to formation and release of new hormone instead of release of previously stored hormone. Since this patient's PBI level had not begun to fall by the time the last specimen was drawn at seventy-two hours after the injection of TSH, a similar study was performed on another subject with potentially normal thyroid function who had been taking 3 grains of thyroid daily for several years, the PBI concentration being determined at 24-hour intervals for five days after a single injection of 5 units of TSH. Her levels rose from a pre-TSH value of 7.5 μg. per 100 ml. to a maximum of 8.2 μg. per 100 ml. by the forty-eighth hour and returned to the pre-injection value by the seventy-second hour, remaining there for the subse-

TABLE 7. LOW THYROID RESERVE—TYPE 3: NORMAL RESPONSE IN THYROIDAL I^{131} UPTAKE, BUT NO RESPONSE IN SERUM PBI LEVEL

	No. of cases
Hypopituitarism	5
After subtotal thyroidectomy (interval 3 mos. to 21 yrs.)	4
for nontoxic nodular goiter 2	
for nontoxic diffuse goiter 1	
for toxic nodular goiter 1	
With subacute nonspecific thyroiditis	4
Six to eight weeks after cessation of prolonged thyroid medication	3
Nontoxic diffuse goiter	3
Two days after cessation of antithyroid drug	2
Nontoxic nodular goiter	1
Functioning adenoma	1
After I^{131} therapy for toxic nodular goiter (interval 11 mos.)	1
Graves' disease in remission (4 yrs. after propylthiouracil stopped)	1
Cushing's syndrome (2 mos. after total adrenalectomy)	1
Growth retardation	1
Total	*27*

quent two days. It therefore appears that the maximum rise due to formation of new hormone occurs between the forty-eighth and seventy-second hours following a single injection of TSH.

Since the ingestion of thyroid in doses sufficiently great to result in a depletion of stored hormone in the gland usually causes a decrease in the initial I^{131} uptake below the normal range, tests on these subjects are not included in the Type 3 group. Other conditions in which tests demonstrated a normal I^{131} response but no significant rise in PBI level are listed in Table 7. It is of interest that all 5 cases of hypopituitarism (Table 8) had initial

TABLE 8. RESULTS OF TSH TESTS IN HYPOPITUITARISM

Test No.	Thyroidal I^{131} uptake (% tracer dose)				Serum PBI (μg./100 ml.)			Remarks
	Pre-TSH (3-hr.)	Post-TSH (3-hr.)	Change	24-hr.	Pre-TSH	Post-TSH	Change	
358	7.9	18.6	+10.7	30.8	2.7	3.3	+0.6	Meningioma
310	7.6	17.6	+10.0	27.1	5.2	2.1	−3.1	Chromophobe adenoma
343	5.9	29.7	+23.8	28.1	3.6	4.2	+0.6	Chromophobe adenoma
419	5.8	28.5	+22.7	18.4	5.2	4.5	−0.7	Chromophobe adenoma
447	6.0	24.4	+18.4	23.5	5.2	5.6	+0.4	Chromophobe adenoma

3-hour and 24-hour thyroidal I^{131} uptakes in the normal range, and that only 2 of the 5 had low pre-TSH serum PBI levels; yet all showed evidence of a lack of stored hormone. None had impressive clinical evidence of hypothyroidism, although the 2 with low PBI levels had suggestive symptoms of lassitude and increased sensitivity to cold.

In most of the conditions listed in Table 7 a lack of stored thyroid hormone is conceivable, but it would be surprising in the cases of untreated nontoxic goiters. Perhaps some of these goiters may be associated with impairment of the physiologic mechanism for storage or release of thyroid hormone. Further studies of this type of case are obviously indicated.

Type 4—*No response in thyroidal I^{131} uptake; low PBI level*

This type is similar to Type 1, the only difference being that the PBI level is low instead of lying in the normal range. It is of special interest, because it demonstrates that a thyroid gland which has a normal I^{131} uptake at both three hours and twenty-four hours can still be unable to make a normal amount of hormone. Such subjects if tested only by their I^{131} uptake, would be reported to be normal; yet they are usually clinically hypothyroid, and results of other tests such as the basal metabolic rate and serum cholesterol level are consistent with mild hypothyroidism. As seen in Table 9, of the 6 cases so far observed, 5 followed I^{131} therapy for Graves' disease. Two of the tests in this table (Nos. 92 and 268) were performed on the same patient, the second being carried out a year after

TABLE 9. LOW THYROID RESERVE—TYPE 4: NO RESPONSE IN THYROIDAL I^{131} UPTAKE AND LOW SERUM PBI LEVEL

Test No.	Thyroidal I^{131} uptake (% tracer dose)				Serum PBI (μg./100 ml.)			Remarks
	Pre-TSH (3-hr.)	Post-TSH (3-hr.)	Change	24-hr.	Pre-TSH	Post-TSH	Change	
69	10.3	9.3	−1.0	17.3	1.4	1.6	+0.2	Idiopathic
92	10.7	12.7	+2.0	25.6	2.8	3.3	+0.5	I^{131} for Graves' disease 2 mos. before
268	9.2	11.5	+2.3	25.0	2.5	3.2	+0.7	Same patient as in test No. 92, one year later
236	7.9	9.6	+1.7	12.9	2.4	2.7	+0.3	I^{131} for Graves' disease 4 mos. before
243	13.1	16.8	+3.7	22.6	2.5	3.3	+0.8	I^{131} for Graves' disease 10 mos. before
245	8.5	13.2	+4.7	16.9	2.2	2.3	+0.1	I^{131} for recurrent Graves' disease 20 mos. before
305	7.3	9.5	+2.2	13.5	1.2	1.3	+0.1	I^{131} for recurrent Graves' disease 3 mos. before

the first without intervening treatment. The results were practically identical and indicate no restoration of normal hormone production. One subject was a graduate nurse in whom idiopathic hypothyroidism was apparently developing. None of these patients has regained normal thyroid function and all have benefited from thyroid medication.

Type 5—*Elevated thyroidal I^{131} uptake; no response in serum PBI level*

This type of response is also of special interest. It occurred in 8 subjects, whose data are listed in Table 10. In most of these the 3-hour I^{131} uptakes

TABLE 10. LOW THYROID RESERVE—TYPE 5: ELEVATED THYROIDAL I^{131} UPTAKE BUT NO RESPONSE IN SERUM PBI LEVEL

Test No.	Thyroidal I^{131} uptake (% tracer dose)				Serum PBI (μg./100 ml.)			Remarks
	Pre-TSH (3-hr.)	Post-TSH (3-hr.)	Change	24-hr.	Pre-TSH	Post-TSH	Change	
128	22.0	22.3	+ 0.3	52.4	7.8	6.9	−0.9	I^{131} for recurrent Graves' disease 11 mos. before. Asymptomatic
129	22.2	27.3	+ 5.1	42.1	4.0	4.5	+0.5	Subtotal thyroidectomy for Graves' disease 2 yrs. before. Asymptomatic
160	20.0	34.3	+14.3	34.9	6.6	5.5	−1.0	I^{131} for recurrent Graves' disease 20 mos. before. Asymptomatic
340	20.6	41.5	+20.9	48.1	4.6	5.4	+0.8	Nontoxic nodular goiter
345	32.2	43.3	+11.1	52.3	4.2	4.8	+0.6	Struma lymphomatosa
368	22.5	32.8	+10.3	51.5	4.5	4.4	−0.1	Acute nonspecific thyroiditis 16 mos. before. Asymptomatic
426	21.6	31.8	+10.2	43.8	4.7	5.0	+0.3	Functioning single adenoma. BMR −15%; serum cholesterol 194 mg./100 ml.
459	25.0	31.0	+ 6.0	49.0	6.1	6.8	+0.7	Recurrent nontoxic diffuse goiter. Subtotal thyroidectomy 8 yrs. before

were only slightly higher than normal and the 24-hour uptakes were in the borderline high range. In all except the first case the I^{131} uptake response was significant, *i.e.*, it was increased by more than 5 per cent of the administered tracer dose; and in 5 it was increased by more than 10 per cent. In the 3 patients who had been treated for Graves' disease and the 2 with thyroiditis (one had struma lymphomatosa diagnosed by needle-biopsy findings, and the other had had an acute nonspecific thyroiditis sixteen months previously) the failure of the serum PBI level to rise was probably due to a lack of stored hormone. Such cases demonstrate, however, that the thyroid gland can be trapping iodide at an increased rate and can even respond further to additional TSH stimulation, yet not be making hormone in sufficient quantities for storage or for the production of an elevated PBI level. In the patient with the functioning adenoma,

the adenoma presumably accounted for the elevated I^{131} uptake, which was 21.6 per cent at three hours and 43.8 per cent at twenty-four hours. However, the output of thyroid hormone was not sufficiently great to cause hyperthyroidism, and the serum PBI level was normal—4.7 μg. and 5.0 μg. per 100 ml. before and after TSH, respectively. The absence of a significant rise in the PBI level probably reflects a lack of stored hormone in the nonadenomatous thyroid tissue and suggests a lack of response by the adenoma itself to TSH stimulation. In the 2 cases of nontoxic goiter, 1 diffuse and 1 nodular, this type of response suggests a disturbance in the mechanism for hormone storage or release, similar to that postulated in the cases of nontoxic goiter with Type 3 responses.

Although some of the findings in Types 2, 3, 4 and 5 were presumably related to an abnormal response in a remnant of thyroid tissue, many were due to other factors. Even in those which were associated with an element of low reserve, this lack was only partial. It therefore seems advisable to limit the term "low thyroid reserve" to cases with Type 1 responses. One must be aware of the other types of response, however, because if TSH tests are performed on the basis of either thyroidal I^{131} uptake alone or serum PBI level alone, it might be difficult to differentiate true low reserve from these other states.

Prognosis

With this clarification of the concept of low thyroid reserve, it became of importance to know whether it represented a transient phase in the status of the thyroid or whether it might be permanent in some instances. TSH tests were therefore repeated at intervals on patients who demonstrated this abnormality. Although the number of cases studied in this manner is not large, sufficient data have been accumulated to furnish an indication of the possibilities.

After subtotal thyroidectomy

In the patients who demonstrated low thyroid reserve after subtotal thyroidectomy:

1. Low reserve may persist for years. The longest interval so far noted was in a patient who had undergone a subtotal thyroidectomy for Graves' disease thirty-four years previously. The TSH test revealed the presence of typical low thyroid reserve.
2. In a person who previously has had Graves' disease, a gland remnant demonstrating low reserve may later demonstrate hyperfunction.

As yet no instances of low reserve becoming normal reserve or progressing to hypothyroidism have been observed in patients who have undergone subtotal thyroidectomy.

TABLE 11. LOW THYROID RESERVE AFTER I^{131} THERAPY: SUBSEQUENT RECURRENCE OF HYPERTHYROIDISM

(Patient G.W., a 45-year-old colored male)

Test No.	Date	Thyroidal I^{131} uptake (% tracer dose)			Serum PBI (μg./100 ml.)		Remarks
		Pre-TSH (3-hr.)	Post-TSH (3-hr.)	24-hr.	Pre-TSH	Post-TSH	
176	Aug. 4, '53	66.9	74.6	64.9	7.8	14.3	Moderately severe Graves' disease
	Aug. 8, '53	5.5 mc. I^{131}					
247	Jan. 26, '54	15.7	18.2	32.9	5.4	5.4	Asymptomatic 5½ mos. after R_x
303	Apr. 27, '54	34.4	43.0	55.6	6.4	7.6	Asymptomatic 8½ mos. after R_x
432	Feb. 9, '55	22.6	47.3	34.4	8.2	9.1	Slightly increased nervousness, unexplained weight loss

After I^{131} therapy

In patients who demonstrated low thyroid reserve following I^{131} therapy for Graves' disease:

1. Low reserve may persist. The longest interval observed to date is six years after administration of the therapeutic dose.
2. In a patient with low reserve, a recurrence of hyperthyroidism may develop later. An example of this sequence of events is shown in Table 11. The TSH test showed that this patient with Graves' disease had a typical low reserve five and a half months after I^{131} therapy, but three months later his I^{131} uptakes were again elevated, and a year later his serum PBI level had risen above normal.
3. A patient with low reserve may later have frank hypothyroidism. In Table 12 is presented an example of such a case. This young woman with Graves' disease had a typical low reserve six months after I^{131} therapy, but four months later her PBI level was subnormal, symptoms of hypothyroidism had developed, and she has required thyroid medication since that time.

TABLE 12. LOW THYROID RESERVE AFTER I^{131} THERAPY; SUBSEQUENT HYPOTHYROIDISM

(Patient E.T., a 22-year-old female)

Test No.	Date	Thyroidal I^{131} uptake (% tracer dose)			Serum PBI (μg./100 ml.)		Remarks
		Pre-TSH (3-hr.)	Post-TSH (3-hr.)	24-hr.	Pre-TSH	Post-TSH	
	Mar. 2, '53			84.5			Moderately severe Graves' disease; acute hepatitis
	Mar. 6, '53	6.5 mc. I^{131}					
190	Sept. 8, '53	12.4	12.3	21.6	4.2	4.1	Asymptomatic 6 mos. after R_x
243	Jan. 19, '54	13.1	16.8	22.6	2.5	3.3	Mild symptoms of hypothyroidism 10 mos. after R_x

As yet no cases have been observed in which there was a return to normal thyroid reserve after I^{131} therapy for Graves' disease.

Thyroiditis

In patients who demonstrated low thyroid reserve during or following thyroiditis:

1. Normal reserve may ultimately be restored. In Table 13 the results of TSH tests in such a case are presented. In this instance normal reserve was restored by the tenth month following an acute attack of nonspecific thyroiditis.

TABLE 13. LOW THYROID RESERVE AFTER THYROIDITIS; SUBSEQUENT RESTORATION OF NORMAL RESERVE

(Patient M.G., a 40-year-old female)

Test No.	Date	Thyroidal I^{131} uptake (% tracer dose)			Serum PBI (μg./100 ml.)		Remarks
		Pre-TSH (3-hr.)	Post-TSH (3-hr.)	24-hr.	Pre-TSH	Post-TSH	
213	Nov. 3, '53	1.7	4.3	1.4	9.8	11.6	Acute nonspecific thyroiditis for 6 wks.
227	Dec. 1, '53	2.8	6.2	8.7	3.0	3.4	Thyroiditis subsiding
265	Feb. 23, '54	12.0	13.2	22.6	4.5	4.6	Asymptomatic
367	Sept. 7, '54	23.0	28.3	44.6	4.3	6.2	Asymptomatic

2. Low reserve may persist. The longest duration in the series to date is five years.
3. Frank hypothyroidism may ultimately develop.

The low reserve state which occurs within eight weeks of cessation of thyroid medication in a person with potentially normal thyroid function has been demonstrated to be a transient phenomenon, subsequent TSH tests being entirely normal.

It is therefore evident that low thyroid reserve may persist indefinitely, or it may be a transient state, later giving way either to a return of normal thyroid function or to definite hypothyroidism.

Clinical Significance

The chief clinical significance of low thyroid reserve is the fact that it may be a cause of mild hypothyroidism which is difficult to diagnose without the TSH test. Approximately 50 per cent of patients with low thyroid reserve (Type 1) had symptoms suggestive of mild hypothyroidism, but the results of customary tests of thyroid function were usually within normal limits. Occasionally an elevated serum cholesterol level would be

the only other finding suggesting thyroid abnormality. In some patients the symptoms of hypothyroidism would come and go without specific therapy, suggesting that the amount of hormone produced by the remnant of thyroid tissue was adequate to meet the body's requirements at some times, but not at others. When symptoms were present, in every instance the administration of desiccated thyroid (usually in doses of 1 grain per day or less) resulted in improvement. In the patients in whom an asymptomatic elevation of the serum cholesterol level was the only other evidence of low thyroid reserve besides the TSH test results, administration of thyroid was considered advisable in order to restore the cholesterol concentration to normal levels. In the absence of clinical symptoms or of hypercholesterolemia, thyroid therapy is probably unnecessary.

DISCUSSION

In addition to aiding in the evaluation of results of TSH tests suggesting low thyroid reserve, these studies have certain physiologic implications. They provide further evidence that the effects of TSH upon the iodide-trapping and the hormone-release mechanisms of the thyroid gland are not necessarily related. Under certain circumstances either one may respond without the other. The occurrence of such responses in some cases of nontoxic goiter suggests that derangements of the mechanisms for storage or release of thyroid hormone can take their place beside iodine deficiency and defects in the ability to synthesize thyroxine as causes for the development of nontoxic goiter.

It is evident from the Type 4 responses that the presence of a normal rate of thyroidal iodide uptake does not imply normal ability to supply thyroid hormone. Furthermore, the finding that in hypopituitarism the thyroid gland's stores of hormone may be low even though the iodide uptake and serum PBI level are normal, suggests that in this condition the rate of formation or storage of hormone is decreased before the other functions of the thyroid gland are affected.

From the data on patients who had been receiving thyroid, it appears that it may take over eight weeks for normal stores of thyroid hormone to be replaced, once they have been depleted. It is also evident that very little of the rise in the PBI level which occurs after a single injection of 5 units of TSH is contributed by formation of new hormone, the great part being due to release of previously stored hormone.

The behavior of remnants of thyroid tissue after subtotal thyroidectomy or damage by irradiation or thyroiditis is of considerable interest. Why some glands will eventually recover normal function or even become hyperfunctioning again, whereas others remain in a state of low reserve indefinitely, is a mystery. Perhaps the presence of a critical amount of

thyroid tissue is necessary for the ability to regenerate. The ultimate outcome in a patient with hyperthyroidism may depend upon the persistence of the factor accounting for the initial development of hyperthyroidism. Whether a patient with treated hyperthyroidism ever regains normal reserve remains to be seen. So far this has not been observed, but the follow-up periods may not have been sufficiently long.

The fact that a condition of low thyroid reserve has been observed to proceed to hypothyroidism following I^{131} therapy or thyroiditis, but not after subtotal thyroidectomy, suggests that persistent damage to the thyroid remnant is necessary for this development to take place.

SUMMARY

Low thyroid reserve is a state in which a remnant of thyroid tissue is able to maintain a normal rate of iodide uptake and a normal serum PBI level while under maximal stimulation by endogenous TSH, but is unable to respond to further stimulation. Low thyroid reserve can be definitely diagnosed only by testing the response of *both* thyroidal I^{131} uptake and serum PBI level to the administration of TSH. A test utilizing the responses of the 3-hour thyroidal uptake of I^{131} and the serum PBI level to a single intramuscular injection of 5 units of TSH has been employed for this purpose. A lack of response of the thyroidal I^{131} uptake to this stimulation may be simulated by previous exposure to iodide, but in such instances a normal rise in the serum PBI level usually occurs. In other cases there may be no increase in the serum PBI level because of lack of stored hormone in the thyroid gland, but in such instances the thyroidal I^{131} response is usually normal.

Although low thyroid reserve has been observed more frequently in patients who have had I^{131} therapy or subtotal thyroidectomy, it has also been seen following thyroiditis and shortly after cessation of prolonged thyroid medication. It may be a transient phenomenon, or it may persist indefinitely. It may be the cause of obscure symptoms of hypothyroidism in patients in whom other tests of thyroid function yield equivocal results. In the presence of symptoms of hypothyroidism or of hypercholesterolemia, treatment with desiccated thyroid is beneficial.

Through the use of the TSH test in patients having suggestive evidence of low thyroid reserve, several observations of physiologic significance with respect to thyroid function have been made. These include:

1. The effects of TSH upon the iodide-trapping and the hormone-release mechanisms of the thyroid gland are not necessarily related.
2. The presence of a normal rate of thyroidal iodide uptake does not imply ability of the gland to supply thyroid hormone in normal amounts.

3. Practically all of the rise in the serum PBI level which follows a single injection of 5 units of TSH results from release of stored hormone, very little being contributed by the formation of new hormone.
4. After the stores of hormone in the thyroid gland have been depleted, it may require over eight weeks for them to be replaced.
5. In hypopituitarism it appears that the rate of formation or storage of hormone is decreased before the other functions of the thyroid gland are affected.
6. Evidence suggests that some types of nontoxic goiter are associated with a derangement in the ability of the thyroid gland to store or to release hormone.

For intelligent evaluation of the results of the TSH test an understanding of these possible determining factors is necessary.

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COMPLICATIONS OF THYROID SURGERY*

OLIVER H. BEAHRS, M.D., ROBERT F. RYAN, M.D.† AND ROY A. WHITE, M.D.†

Section of Surgery, Mayo Clinic and Mayo Foundation,‡ Rochester, Minnesota

THE various complications of thyroid surgery have long been known to surgeons embarking on the surgical treatment of goiter. These complications may be severe enough to jeopardize the life of the patient or to create a physical or physiologic incapacity which will limit his normal activities. Because of the severity of these complications it becomes necessary that their incidence be reduced to an absolute minimum in this age of modern surgery. Moreover, if surgery is to continue to play a dominant role in the treatment of thyroid disease, the complications of this form of treatment must be less than those of other equally effective forms of treatment.

Surgery of the thyroid gland has a long history, and the earliest accounts contain references to the complications. McGovern's (1) paper contains the statement that the first extirpation of the goiter was performed in Baghdad in the latter part of the tenth century by Abdul or Albucasis "who knew very well how to control hemorrhage by ligature and hot iron." McGovern (1) also stated that the first extirpation of a goiter carried out in America was by Smith in Maryland in 1835. An interesting account of the Mayo brothers' first thyroid operation performed in 1890 is included in their biography by Clapesattle (2). The patient had an enormous goiter which was causing symptoms of severe pressure. The goiter was scooped out and hemorrhage controlled by large sponges saturated with turpentine. These were left in the wound and removed several days later.

As surgeons learned to control hemorrhage from the gland, more aggressive operations were undertaken and two other complications became evident, namely, paralysis of the vocal cord and tetany. Meurman (3) quoted from Wölfler's report of 1882 from Billroth's clinic that 13 of 44 thyroidectomized patients had paralysis of the vocal cord.

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† Fellow in Surgery, Mayo Foundation.

‡ The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

According to Halsted (4) the classic work of Kocher associated tetany as a complication of thyroid surgery, but it was not until the work of Vassale and Generali (5) that this complication was associated with extirpation of the parathyroid glands secondary to removal of the goiter.

The hazards of operating on the patient with hyperthyroidism were recognized early by all workers in the field and accounted for the development of multiple-stage and conservative procedures in the management of these cases. The hazards of operating on patients with toxic goiter became less after Plummer, in 1923 (6, 7), introduced the use of iodine in their preoperative preparation. The management of thyroid crisis in days gone by taxed the ingenuity of the surgeon and the crisis was a harrowing experience for the few patients who survived it. In a recent report McArthur and associates (8) stated that of 36 thyroid storms seen between 1921 and 1946, inclusive, at the Massachusetts General Hospital, 25 followed a surgical procedure and carried a mortality rate of 64 per cent.

The dangers of infection and pneumonia were ever present among patients undergoing thyroid surgery.

MORTALITY

Our surgical forebears should have our everlasting respect for developing the field of thyroid surgery in the presence of the problems which confronted them. Kocher, quoted by Mayo (9), indicated that the mortality rate prior to 1850 was 40 per cent in operative cases. By 1883 it had decreased to 15 per cent, and at the time of Mayo's report in 1905 it was 3 per cent. Kocher, by that time, had reduced his own mortality rate to 0.2 per cent.

In the present study we have reviewed the mortality statistics and cause of death in patients operated on for thyroid disease during the past sixteen years (1940 to 1955, inclusive) and have carefully evaluated the complications experienced in all cases in which operation was performed in 1954, the most recent year in which all information was available at the time of preparation of this report. Complications seen in patients on whom total thyroidectomy was carried out in the period from 1952 through 1954 also are included.

During the sixteen-year period, 14,374 thyroidectomies had been performed and 46 of the patients died during hospitalization. The series has been divided into two parts: cases in which operation was performed in the period 1940 to 1945 inclusive (Table 1), and in the period 1946 to 1955 inclusive (Table 2). This division has been made because, beginning about 1946, the death rate has been obviously reduced. This undoubtedly is the result of more careful selection of patients and the availability of antibiotic agents. The seriously ill patient is less frequently operated upon

TABLE 1. HOSPITAL MORTALITY ASSOCIATED WITH THYROID SURGERY: 1940 TO 1945, INCLUSIVE

Year	Exophthalmic goiter		Adenomatous goiter with hyperthyroidism		Adenomatous goiter without hyperthyroidism		Malignant lesions		Miscellaneous lesions and conditions*		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1940	305	3	217	5	231		30	3	14		797	11
1941	332	3	200	2	260	1	25		21		838	6
1942	326	2	253	1	252		24		28		883	3
1943	363	2	262	5	286	1	29	1	18		958	9
1944	341	2	237	1	364		27		19		988	3
1945	302	1	214	2	362	1	34	1	26		938	5
Total	*1,969*	*13*	*1,383*	*16*	*1,755*	*3*	*169*	*5*	*126*	*0*	*5,402*	*37 (0.7 per cent)*

* Including thyroiditis, colloid goiter and miscellaneous lesions.

until his condition has improved sufficiently to permit surgery at less risk.

In the earlier series there were 37 deaths in 5,402 thyroidectomies for a mortality rate of 0.7 per cent, whereas in the last ten years there were only 9 fatalities in 8,972 surgical procedures for a mortality rate of 0.1 per cent. In the total series the mortality rate was 0.3 per cent.

As will be noted in Tables 1 and 2, the largest number of deaths occurred in the group of patients with adenomatous goiter with hyperthyroidism: 20 deaths in 2,539 thyroidectomies. Only 4 of these occurred in

TABLE 2. HOSPITAL MORTALITY ASSOCIATED WITH THYROID SURGERY: 1946 TO 1955, INCLUSIVE

Year	Exophthalmic goiter		Adenomatous goiter with hyperthyroidism		Adenomatous goiter without hyperthyroidism		Malignant lesions		Miscellaneous lesions and conditions*		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1946	260	1	218	1	375		34		31		918	2
1947	195		116		361		41	1	34		747	1
1948	156		162		297		38		33		686	
1949	161		109		419		56		57		802	
1950	192		110		474		49		70		895	
1951	155		110	1	574		55		98		992	1
1952	146		78		613		54		105	1	996	1
1953	113		89		617		64		96		979	
1954	126		96	2	566	1	88	1	145		1,021	4
1955	79		68		623		64		102		936	
Total	1,583	1	1,156	4	4,919	1	543	2	771	1	8,972	9 (0.1 per cent)
Total (1940–1945)	1,969	13	1,383	16	1,755	3	169	5	126	0	5,402	37 (0.7 per cent)
Both series	*3,552*	*14*	*2,539*	*20*	*6,674*	*4*	*712*	*7*	*897*	*1*	*14,374*	*46 (0.3 per cent)*

* Including thyroiditis, colloid goiter and miscellaneous lesions.

the decade 1946 through 1955. During this latter period only 1 of the 1,583 patients with exophthalmic goiter who underwent thyroidectomy died during hospitalization and this occurred in 1946. It is interesting to note the gradual decline in the number of patients undergoing operation for exophthalmic goiter as shown in Tables 1 and 2. Approximately the same number of patients with Graves' disease have been seen each year at the Mayo Clinic. For the most part the patients not operated upon have received radioactive iodine therapy as definitive treatment. In the cases of adenomatous goiter without hyperthyroidism there has been only 1 death in 4,919 thyroidectomies in the recent ten-year period (Table 2). This patient was 70 years of age, had a large goiter causing pressure symptoms and died of a cerebrovascular accident during the postoperative period.

TABLE 3. HOSPITAL MORTALITY AND CAUSE OF DEATH IN THYROID SURGERY: 1940 TO 1945, INCLUSIVE

Year	Number of thyroid procedures	Cause of death							Hospital deaths	
		Cardiac failure	Pulmonary embolism	Airway complications	Pneumonia	Infection	Thyroid crisis	Carcinoma	Number	Per cent
1940	797	2	2	1	6				11	1.4
1941	838	2		1	3				6	0.7
1942	883	3							3	0.3
1943	958	3		1	2	1	1	1	9	0.9
1944	988	1	1				1		3	0.3
1945	938		1		3	1			5	0.5
Total	*5,402*	*11*	*4*	*3*	*14*	*2*	*2*	*1*	*37*	*0.7*

The various causes of death have been listed in Tables 3 and 4. It is interesting to note that 14 deaths resulted from pneumonia and 2 from wound infections in the earlier period, whereas no deaths from these causes occurred among the patients operated on in the period 1945 through 1955. This probably reflects the availability and use of antibiotics. Cardiac failure was the commonest cause of death in our present series, occurring 5 times in patients with hyperthyroidism (Table 4). Death from airway complications occurred on 2 occasions; in retrospect, 1 of these deaths was possibly preventable. Two deaths occurred from thyroid crisis after operation, 1 each in 1943 and 1944. Death did not occur from this cause in the last eleven years.

In 2,739 patients operated upon because of hyperthyroidism, from 1946 to 1955 inclusive, there were 5 deaths. This compares with the report by Cattell (10) in which he reported 5 deaths after operation on 2,700 patients with hyperthyroidism. The 5 deaths in our series were the result of cardiac complications. Because of the availability of medical forms of treat-

TABLE 4. HOSPITAL MORTALITY AND CAUSE OF DEATH IN THYROID SURGERY: 1946 TO 1955, INCLUSIVE

Year	Number of thyroid procedures	Cause of death				Hospital deaths	
		Cardiac failure	Pulmonary embolism	Airway complications	Cerebrovascular accident	Number	Per cent
1946	918	2				2	0.2
1947	747			1		1	0.1
1948	686					0	0
1949	802					0	0
1950	895					0	0
1951	992	1				1	0.1
1952	996		1			1	0.1
1953	979					0	0
1954	1,021	2		1	1	4	0.4
1955	936					0	0
Total	*8,972*	*5*	*1*	*2*	*1*	*9*	*0.1*

ment—mainly radioactive iodine—it is possible that certain high-risk patients with cardiac complications may be treated with drugs in the future and further reduction in the mortality rate from surgical treatment may be effected. However, physicians must be ever aware that there is also a mortality rate associated with nonsurgical forms of treatment, and patients should not be denied the benefits of surgical procedures if, in the opinion of the internists and surgeons seeing the patient, there is less risk in operating than in not operating.

The risk of operating on a patient with an adenomatous goiter without hyperthyroidism, primarily for prevention of the potential hazards of a nodular goiter, should be close to zero. Rarely, however, irrespective of careful selection and surgical precautions, a patient may be lost due to causes unrelated to thyroid surgery.

Carcinoma of the thyroid gland will probably cause the highest mortality rates. In 712 patients operated on for malignant lesions there were 7 deaths; all 7 deaths were associated with airway or pulmonary complications related to the cancer. Most deaths directly related to the surgical procedure should be preventable, but those due to irreversible damage of the tumor usually cannot be prevented.

COMPLICATIONS

The important complications of thyroid surgery today remain the same as those in Kocher's day; however, they occur less frequently and the in-

cidence of those associated with infection, that is, wound suppuration and pneumonia, has been greatly reduced. Hemorrhage in the immediate postoperative period remains a most serious problem, primarily because of jeopardy to the airway as pressure increases beneath the strap muscles. The onset of tracheal obstruction can be most dramatic and the results most disastrous.

Paralysis of the vocal cords and parathyroid tetany account for the major number of complications following thyroid procedures. Huppler and associates (11) reported a series of cases observed in the Mayo Clinic, in which paralysis of the vocal cords was present after operation elsewhere. Of 272 patients seen after thyroidectomy over a ten-year period (1939 to 1948, inclusive) 141 had bilateral cord paralysis, 66 paralysis on the right, and 65 on the left. Ranke and Holinger (12) recently have written on paralysis of vocal cords following thyroidectomy and the association of paralysis with hypothyroidism in 31 per cent of their cases and hypoparathyroidism in 16 per cent. Unilateral paralysis has been reported by Holinger (13) to occur in as high as 15 per cent of cases; reports by Lahey and Hoover (14) indicate an incidence of 0.3 per cent and Wade (15) reported an even lower incidence. The incidence of bilateral cord paralysis in most reports is less than 1 per cent (Holinger (13)).

Tetany secondary to thyroidectomy has generally been reported to occur in 1 to 3 per cent of patients. Bartels (16) has reported that tetany developed in 70 of 2,300 patients, an incidence of 3 per cent. However, the incidence of permanent tetany was only 0.69 per cent. Swinton (17) has reported that in large clinics hypoparathyroidism has developed after thyroidectomy in 0.5 to 1.5 per cent of the patients. Buckwalter and associates (18), in a recent paper, reported 18 cases of tetany after 600 operations on the thyroid gland—an incidence of 3 per cent.

Myxedema is not a serious complication of thyroid surgery, since it can be treated so easily and has variously been reported to occur in 1 to 7 per cent of the cases; the incidence varies considerably, depending on the type of goiter. It is most frequently seen in cases of thyroiditis.

To evaluate the current morbidity associated with thyroid surgery, histories of all patients operated on in the year 1954 were carefully reviewed. Thyroidectomy was performed in 1,021 instances. The various types of pathologic diagnoses for 1954 are to be found in Table 2. All patients had an examination of the vocal cords before operation, after thyroidectomy on the day of operation, and again one to two weeks later. In this manner only can accurate information regarding function of the vocal cords be obtained. Inspection of the cords in each case was carried out by a member of the Section of Plastic Surgery and Laryngology. Patients with hyperthyroidism were prepared preoperatively, for the most part, with Lugol's solution; 10 drops were given three times a day, for

seven to ten days prior to operation. In only a few instances was an antithyroid drug or radioactive iodine also administered for preoperative preparation.

With few exceptions, local anesthesia was used. The superficial cervical block and local infiltration were carried out by an anesthesiologist. During the operation nitrous oxide was given and the patient was awakened when necessary in order that the airway might be evaluated. In a few cases a general anesthetic (sodium pentothal) and an intratracheal tube were used. The average hospitalization was four days, the range varying from three to ten days. Most patients were dismissed from our care between the seventh and tenth day after operation.

Paralysis of vocal cords. All patients in this series of 1,021 thyroidectomies had an examination of the vocal cords before operation, after thyroidectomy on the day of operation, and again one to two weeks later. A summary of the information obtained is given in Table 5.

In 10 patients abnormalities were noted before operation. Five patients had paralysis of the right cord and 4, of the left. Six of these patients had carcinoma and another had undergone thyroidectomy previously. One patient with an asymptomatic adenomatous goiter without hyperthyroidism had unexplained paralysis of both vocal cords. The cords remained in a partially adducted position and the airway was adequate.

TABLE 5. DATA ON ABNORMALITIES OF VOCAL CORDS IN 1,021 THYROIDECTOMIES

		Number of patients
Preoperative paralysis:		10
Carcinoma	6	
Recurring adenomatous goiter	1	
Adenomatous goiter (1 bilateral)	3	
Intentional sacrifice of recurrent laryngeal nerve (all carcinoma)		10
Airway questioned or paralysis known to be temporary (2 cases bilateral)		35
Sacrifice or injury known or thought to be permanent:		26
Exophthalmic goiter	2	
Adenomatous goiter	16	
Carcinoma	3	
Miscellaneous	5	
Percentage of sacrifice or injury (26 of 2,002 nerves)		1.3 per cent

In 10 patients the recurrent laryngeal nerve (5 right and 5 left) was intentionally sacrificed in the course of the operation on the thyroid. In each instance the pathologic diagnosis was carcinoma and the operation was definitive in type.

Normal function of the vocal cords was questionable in 35 patients. However, on examination immediately after operation or one to two weeks later, motion of the vocal cords was found to be normal. In some of these patients edema of the larynx or lack of co-operation of the patient in the immediate postoperative period did not permit an adequate examination of the vocal cords, or a vocal cord was found not to move temporarily but on subsequent examination during the postoperative period prior to the patients' dismissal the vocal cords moved normally and the airway was adequate.

In 26 patients, on both postoperative examinations, 1 vocal cord (11 right and 15 left) was found to be fixed. In these cases it is assumed that paralysis is permanent. A few of these patients have been seen subsequently and on laryngoscopic examination months later the vocal cord has remained fixed. The majority have not been seen for later re-examination. However, on the basis of follow-up examination on the aforementioned group of 35 patients who were known to have had temporary paralysis or malfunction of a vocal cord, it is reasonable to assume that function of the vocal cords of a few of the 26 patients will return to normal. We prefer not to evaluate the postoperative condition of these patients other than by our own examinations. If we accept the cords in all these cases as being permanently fixed, the incidence of unintentional or accidental injury to recurrent laryngeal nerves is 1.3 per cent of 2,002 nerves exposed to jeopardy. In no patient was there unexpected bilateral paralysis of the vocal cords.

Thyroidectomies at the Mayo Clinic are performed primarily by a group of five general surgeons, each using his own technic. Several surgeons routinely expose the recurrent nerves in the course of the dissection, whereas the others do not. Two surgeons ligate the inferior thyroid artery outside the capsule of the gland. All surgeons, except in a few cases, use local anesthesia and rely on the adequacy of the airway and the sound of the voice, in part, to determine vocal function. The incidence of accidental injury to the recurrent nerve is proportionately equal among these surgeons. Whether or not the surgeon elects to expose the nerve, as recommended by some, accurate anatomic knowledge of its location is required, and every surgeon operating on the thyroid gland must be constantly aware of the problems related to injury to the nerve (Lahey and Hoover (14) and Wade (15)).

Intentional sacrifice of a recurrent laryngeal nerve in the presence of carcinoma of the thyroid gland is always justified if the nerve is grossly

involved by the tumor or if it becomes necessary to remove the nerve in order to resect the cancerous lesion adequately and safely.

Tracheotomy. A temporary prophylactic tracheotomy was established in 11 patients. The reasons for this were primarily the hazard of tracheal collapse (Mayer (19) and Marangos (20)) after the removal of a large goiter causing pressure on and erosion of the tracheal cartilages, and obstruction from invasion by carcinoma. In only 2 patients was the tracheotomy established because of a question of an inadequate airway secondary to injury to a recurrent nerve.

Two emergency tracheotomies were established during the course of thyroidectomy because of inadequacy of the airway secondary to laryngospasm. Two other emergency tracheotomies were performed during the immediate postoperative period, both secondary to pressure on the trachea due to secondary hemorrhage.

A tracheotomy should be used whenever there is a real question of inadequacy of the airway as a result of prolonged spasm, edema, bilateral cord paralysis or secondary hemorrhage. A tracheotomy is well tolerated and prevents a real and dramatic hazard to the life of the patient. The condition of thyroidectomized patients should be followed carefully during the immediate postoperative period because of the danger of secondary hemorrhage and jeopardy of the airway due to pressure of accumulated blood beneath the strap muscles.

FURTHER COMPLICATIONS

Hemorrhage. In this series of 1,021 thyroidectomies, 2 patients were re-explored because of secondary hemorrhage. In another patient a large hematoma had developed beneath the skin flaps; it was drained without re-exploration. In all patients, with few exceptions, one or two small soft Penrose drains are left in the operative region at the time of operation and are removed on the first or second postoperative day. A drain of this type does no harm and in a few cases it will prevent the occurrence of pressure hematomas which can cause a sudden crisis for the patient and surgeon. It also serves as a telltale for bleeding.

Myxedema. Myxedema is known to have developed in 48 patients in this series (Table 6). No follow-up effort was made, for it would be impossible to establish the diagnosis without the benefit of an examination. Of the patients who were re-examined subsequently, 48 had clinical and laboratory evidence of myxedema. Twelve had been operated on for exophthalmic goiter, which represents at least 10 per cent of the 126 patients who underwent thyroidectomy for this type of goiter. Myxedema is known to have developed in 5 of 566 patients who underwent thyroidectomy for adenomatous goiter without hyperthyroidism. Likewise, hypo-

thyroidism developed in 5 of 88 patients with carcinoma; 3 of these patients had had total thyroidectomy. Of 90 patients operated on in whom the pathologic diagnosis was thyroiditis, myxedema had developed in 26, or approximately 30 per cent.

In patients having subtotal thyroidectomy, myxedema is a complication of surgical intervention, although it is recognized that many patients with a diagnosis of thyroiditis subsequently would become hypothyroid regardless of the operation. In spite of the fact that this is not a serious complication, since it can be so easily controlled, danger exists in that the

TABLE 6. OCCURRENCE OF MYXEDEMA AFTER THYROIDECTOMY (1954)*

	Cases	
	Total	Myxedema
Exophthalmic goiter	126	12
Adenomatous goiter with hyperthyroidism	96	0
Adenomatous goiter without hyperthyroidism	566	5
Carcinoma	88	5†
Thyroiditis	90	26
Miscellaneous	55	0
Total cases	*1,021*	*48*

* No follow-up effort made in patients not seen since thyroidectomy.

† Three patients had had total thyroidectomy; other patients with total thyroidectomy were treated with desiccated thyroid without allowing myxedema to develop.

condition may go unrecognized and that the patient will suffer the incapacities of hypothyroidism. Certainly in operating on patients with benign goiter and selected patients with carcinoma the surgeon should strive to preserve sufficient thyroid tissue so that the occurrence of myxedema will be minimal. Usually we strive to preserve a remnant of thyroid tissue equal to about a fourth of a thyroid gland of normal size (5 Gm. of tissue) in the presence of parenchymatous hypertrophy, at least that amount in cases of adenomatous goiter, and a third to a half of a lobe of normal size on each side in cases of thyroiditis. In patients with thyroiditis this will not necessarily prevent the development of myxedema.

Tetany. The condition of each patient in the series was followed carefully during the postoperative period for the possible development of hypoparathyroidism. Clinical symptoms of tingling and carpopedal spasm were looked for, and attempts were made to elicit Chvostek and Trousseau signs. In patients in whom the development of tetany was anticipated, estimations of the concentration of calcium and phosphorus in the blood

were obtained. Only patients with abnormal findings and requiring treatment were considered to have tetany. The condition of patients during replacement therapy was followed for varying periods. Eleven patients were considered to have permanent tetany. Four of these had had total thyroidectomies because of carcinoma. Five of the 11 were patients with

TABLE 7. OCCURRENCE OF TETANY AFTER THYROIDECTOMY IN 1,021 CASES (1954)

	Total cases	Tetany after partial thyroidectomy		Tetany after total thyroidectomy	
		Temporary	Permanent	Temporary	Permanent
Exophthalmic goiter	126				
Primary		2	1	—	—
Recurrent		—	3	—	—
Adenomatous goiter with hyperthyroidism	96				
Primary		1	—	—	—
Recurrent		—	—	—	—
Adenomatous goiter without hyperthyroidism	566				
Primary		4	1	—	—
Recurrent		—	—	—	—
Carcinoma	88				
Primary		1	1	—	4
Recurrent		—	1	1	—
Miscellaneous	145				
Primary		1	—	—	—
Recurrent		—	—	—	—
Total	*1,021*	*9*	*7*	*1*	*4*

benign goiter, an incidence of 0.5 per cent. If the 3 cases in which the patient was operated on for recurrent exophathalmic goiter be subtracted, the incidence of unexpected permanent tetany after primary thyroidectomy for benign goiter is 0.2 per cent.

In addition to the patients who had permanent tetany there were 10 patients in whom temporary hypoparathyroidism requiring active treatment developed (Table 7). One of the 3 patients had had total thyroidec-

tomy for carcinoma. Each of these patients had clinical findings of tetany and hypocalcemia. The symptoms disappeared and the concentration of calcium in the blood returned to normal on treatment. During observation or follow-up periods, which varied from two weeks to three months, treatment was discontinued in each of these cases. The patients remained symptom-free and the concentration of calcium in the blood remained within the normal range.

In carrying out a routine thyroidectomy the surgeon should take every precaution to protect the parathyroid glands. A rim of the posterior capsule of each lobe should be preserved, as in so doing the parathyroid glands are usually preserved (21), but the surgeon should always be on the lookout for these glands. We do not routinely expose the parathyroid glands in the course of dissection for a subtotal thyroidectomy, but when a gland is seen, care is taken to preserve it, as well as the blood supply to it. When total thyroidectomy is being performed for carcinoma, an effort is made to identify and preserve all parathyroid tissue unless in so doing the primary purpose of the operation, that is, removal of the carcinoma, is jeopardized. If a gland is accidentally removed or is excised purposely in removing a tumor, but otherwise is normal then it should be transplanted to muscle with the hope that it will survive and prevent the development of tetany. In a series of 27 total thyroidectomies performed in the period 1952 to 1954, inclusive, tetany did not develop in 11 patients; 3 patients had transient tetany and 13 were considered to have permanent hypoparathyroidism and required continued treatment. In 3 of the last group, parathyroid glands were transplanted, but in no instance did the tissue function even if it remained viable.

Other complications occurring in the postoperative period included auricular fibrillation of a sufficient degree to warrant active treatment in 5 patients—2 with exophthalmic goiter and 3 with adenomatous goiter with hyperthyroidism. In 1 patient in the series spontaneous pneumothorax (Thomas and Betts (22)) developed, requiring aspiration. Recovery was uneventful. Toxic postoperative psychosis (Brockman and Whitman (23) and Carpelan (24)) developed in another patient.

Cardiac arrest occurred in 1 patient at the completion of the thyroidectomy, while she was being prepared for a secondary dilatation and curettage. Immediate thoracotomy with cardiac massage was performed and fortunately the patient recovered fully without complications.

Complications secondary to injury of the external branch of the superior laryngeal nerve, as described by Moran and Castro (25) and Meurman (3), could not be evaluated in reviewing the histories. Recurrence of hyperthyroidism was not evaluated because of the shortness of the period since operations in 1954.

SUMMARY

In any type of treatment for any type of disease the physician should always have as one aim the reduction of mortality and morbidity to the absolute minimum. In doing this, however, he should always offer the patient the benefits of the treatment which will afford the best chances of cure.

Thyroidectomy is a well established and safe form of treatment for goiter and should remain in the armamentarium of physicians in caring for patients with this disease.

The mortality rate in the ten-year period 1946 through 1955 in 9,000 thyroidectomies at the Mayo Clinic was 0.1 per cent. The complications are reviewed for the year 1954, during which time 1,021 thyroidectomies were performed. The incidence of unintentional paralysis of the vocal cords was 1.3 per cent. Tetany, which was not anticipated, occurred in only 0.2 per cent of patients undergoing primary thyroid operation for benign goiter. Myxedema occurred postoperatively in at least 30 per cent of the patients with thyroiditis. Hemorrhage in 2 patients, toxic psychosis in 1, obstruction of the airway in 2, and cardiac arrest in 1 were the only other significant complications. Fifteen tracheotomies were established prophylactically or as emergency procedures to alleviate airway problems.

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PHYSIOLOGIC ACTIVITY OF TRIIODO- AND TETRAIODOTHYROACETIC ACID IN HUMAN MYXEDEMA*†

JACOB LERMAN, M.D. AND ROSALIND PITT-RIVERS, PH.D.

The Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts, and the National Institute for Medical Research, Hampstead, London, England

IN AN effort to elucidate the role of the different portions of the thyronine nucleus in determing the physiologic activity of thyroxine, compounds have been made embodying substitution in the alanine side-chain. The activity of some of these compounds has been determined under various experimental conditions and in human myxedema. In 1952 Lerman, Harington and Means (1) reported on the activity of some of these analogues in myxedema. In 1953 Pitt-Rivers (2) described the action of the acetic-acid derivatives in animals. The extensive review by Selenkow and Asper (3) brings the subject up to date. In general the results have shown that analogues with substitutions in the alanine side-chain behave qualitatively like thyroxine or triiodothyronine, but quantitatively are weaker. The work of Thibault and Pitt-Rivers (4) indicating that the acetic-acid analogues of thyroxine and triiodothyronine behave differently from other analogues has led to our investigation of the effect of these acetic-acid derivatives in human myxedema. A preliminary report has already been made (5).

The present report deals with results obtained from daily single injections of triiodothyroacetic acid (triac) and tetraiodothyroacetic acid (tetrac) in patients with myxedema, and also with the effect of a single intravenous injection measured over an eight-hour to ten-hour period.

METHODS AND MATERIAL

In all, 5 patients with myxedema received daily doses of triiodothyroacetic acid in varying amounts for periods ranging from twelve to sixteen days.[1] In some cases the

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[1] Some of the material used in these experiments was supplied to us through the kindness of Dr. Robert Kroc of the Warner-Chilcott Laboratories, Morris Plains, New Jersey.

initial dose was small and was gradually increased over the period of observation; in others the initial dose was large and was decreased during the period of treatment. A sixth patient with myxedema received daily doses of tetraiodothyroacetic acid for fourteen days. In each case an electrocardiogram was obtained and the level of serum protein-bound iodine, of blood cholesterol, and the urinary excretion of creatine were determined before and after treatment. In addition, various aspects of the clinical response were observed. In 2 patients with myxedema the effects of a single dose of triiodothyroacetic acid or tetraiodothyroacetic acid were observed for a period of eight to ten hours, the basal metabolic rate being obtained at one-hour to two-hour intervals. In each case a control basal metabolic rate curve was obtained before any injection was given. One of these patients was tested at different times with triiodothyroacetic acid, tetraiodothyroacetic acid and *l*-thyroxine.

RESULTS

In Figure 1 are depicted the results of assay on 5 patients with myxedema receiving daily doses of triiodothyroacetic acid. The standard of comparison is the response of myxedematous subjects to daily intravenous administration of 0.5 mg. of iodine in the form of *dl*-thyroxine polypeptide and equivalent to 0.4 mg. of *l*-thyroxine daily. Patient M. D., receiving an average daily dose of 1.32 mg., showed little or no metabolic response. The initial dose was 0.4 mg. and it was gradually increased to 4.0 mg. Patients

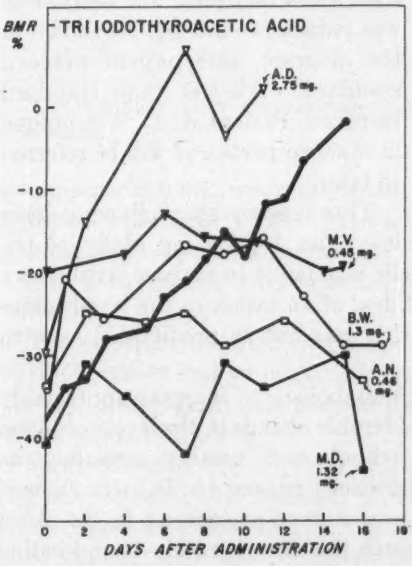

FIG. 1. The response of 5 patients with myxedema to the daily administration of triiodothyroacetic acid intravenously. The dosage was variable.* The heavy line is the standard response of patients with myxedema to the daily administration of 0.5 mg. of iodine in the form of thyroxine polypeptide and equivalent to 0.4 mg. of *l*-thyroxine.

* The average daily dose for each patient is listed in the chart. Individual dosage schedules were as follows:

Patient M. D.—0.4 mg. for 7 days; 0.8 mg. for 2 days; 1.0 mg. for 2 days; 2.0 mg. for 4 days; 4.0 mg. for 2 days.

Patient A. N.—0.1 mg. for 2 days; 0.2 mg. for 3 days; 0.4 mg. for 4 days; 0.6 mg. for 5 days; 1.0 mg. for 2 days.

Patient B. W.—Figure 2.

Patient M. V.—0.25 mg. for 4 days; 0. 4 mg. for 4 days; 0.6 mg. for 7 days.

Patient A. D.—4.0 mg. for 4 days; 2.0 mg. for 8 days.

A. N. and M. V., each receiving about the same average daily dose (0.46 mg. and 0.45 mg., respectively) also showed little or no metabolic response. In Patient A. N. the initial dose of 0.1 mg. was increased gradually to 1.0 mg. daily; in Patient M. V. the initial dose of 0.25 mg. was increased to 0.6 mg. daily. The data on the fourth patient, B. W., are depicted in more detail in Figure 2. Starting with a daily dose of 2.0 mg. of triiodothyroacetic acid intravenously for three days, reduced to 1.5 mg. for the following four days, the basal metabolic rate made a standard response during this period of time. When the dose was reduced to 1.0 mg. daily, the basal metabolic rate dropped to nearly its initial level. This response is in contrast to that of Patient M. D. (Fig. 1), who received the same total dose and whose basal metabolic rate failed to rise as the dose was increased to 4.0 mg. A fifth patient, A. D., received initially a daily dose of 4.0 mg. of triiodothyroacetic acid for four days. In the eight days following, the daily dose was reduced to 2.0 mg. As shown in the diagram, this patient made a standard, or better than standard response. Patient A. D. was unique in other respects and will be referred to later.

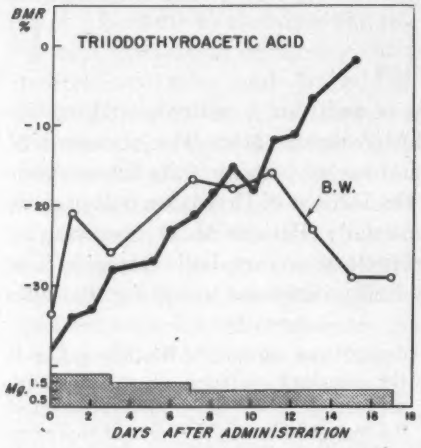

FIG. 2. The response of Patient B. W. (thin line and circles) to daily doses of triiodothyroacetic acid. The heavy line is the standard shown in Figure 1.

Thus it seems that following doses less than 1.0–1.5 mg. daily of triiodothyroacetic acid, the basal metabolic rate failed to make a satisfactory response. In general there was a good deal of variation in the basal metabolic response in any given case, and it was not as predictable as with thyroxine.

In spite of the failure of the basal metabolism to increase appreciably in 4 of the 5 patients, there was a considerable change in the levels of blood cholesterol, serum protein-bound iodine[2] and urinary creatine, as shown in Table 1. It is interesting that the only patient (A. D.) who showed a good response to triiodothyroacetic acid showed an increase in the blood cholesterol level after treatment, although the serum protein-bound iodine level rose from 1.0 gamma to 9.0 gamma per 100 ml. and the urinary

[2] Determinations were made on blood samples drawn between eighteen and twenty hours after the last intravenous injection of the test material.

creatine from 43 mg. to 248 mg. per twenty-four hours. As an explanation of this phenomenon Dr. S. Postal (6) has suggested that under certain conditions the rate of cholesterol synthesis induced by thyroid hormone may be greater than the rate of destruction of cholesterol induced by this hormone.

It should be noted that the serum protein-bound iodine levels observed at the end of the assays did not reflect the character of the response. For example, Patient B. W., who showed a fairly good rise in the basal metabolic rate for the first eight to ten days of the assay (Fig. 2), had a very slight rise in the level of protein-bound iodine from 0.9 gamma to 1.7

TABLE 1. CHANGES IN BLOOD CHOLESTEROL LEVEL, SERUM PROTEIN-BOUND IODINE LEVEL AND URINARY EXCRETION OF CREATINE INDUCED BY TRIIODOTHYROACETIC ACID AND TETRAIODOTHYROACETIC ACID IN PATIENTS WITH MYXEDEMA

Patient	Cholesterol (mg./100 ml.)		PBI (μg./100 ml.)		Creatine (mg./24 hrs.)	
	Before	After	Before	After	Before	After
A.N.	570	404	0.7	4.4		
M.D.	533	258	0.5	11.5		
A.D.	339	377	1.0	9.0	43	248
B.W.	372	192	0.9	1.7		428
M.V.	378	294	1.8	3.6	44	424
M.B.*	372	250	0.8	43.0	72	237

* This patient received tetraiodothyroacetic acid; all the others received the triiodo compound.

gamma per 100 ml.; whereas Patient M. D., who showed little or no metabolic response, had a rise in the level of protein-bound iodine from 0.5 gamma to 11.5 gamma per 100 ml. The rise in urinary creatine excretion was as great as might be expected following an adequate dose of thyroid hormone.

The electrocardiogram in each case showed an increase in amplitude of the T waves and an increase in voltage at the end of treatment. There was a 3 to 4 kilogram weight loss in each case and a diminution in the myxedematous appearance.

Figure 3 shows the response of a patient with myxedema to tetraiodothyroacetic acid. This patient, M. B., made a near standard response to an average daily dose of about 6.0 mg. intravenously. There was also a good clinical response. As shown in Table 1, the blood cholesterol level dropped from 372 mg. to 250 mg. per 100 ml., and the urinary creatine rose from 72 mg. to 237 mg. per twenty-four hours. It is difficult to explain the high value of 43 gamma per 100 ml. for serum protein-bound

iodine concentration at the end of medication. The blood was drawn approximately fifteen hours after the last dose of tetraiodothyroacetic acid. It may mean that this compound disappears for the circulation rather slowly.

Since the results reported by Thibault and Pitt-Rivers (4) suggest that the actions of triiodothyroacetic acid and tetraiodothyroacetic acid in animals and in experiments with kidney slices are rapid in onset and short in duration, we observed the effects of these compounds over an eight-hour to ten-hour period after a single intravenous dose. Figure 4 shows the results in Patient M. R. of a single 2.0-mg. dose of triiodothyroacetic

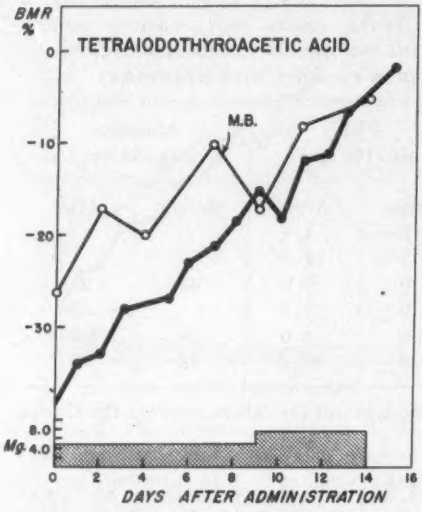

FIG. 3. The response of Patient M. B. (thin line and circles) to the daily intravenous administration of tetraiodothyroacetic acid. The dose was 5 mg. in the first nine days and 8 mg. in the subsequent five days. The heavy line is the standard shown in Figures 1 and 2.

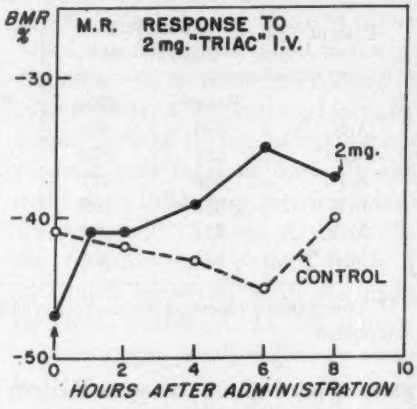

FIG. 4. The response of a patient with myxedema to a single dose of 2 mg. of triiodothyroacetic acid intravenously observed over a period of eight hours, under conditions of fasting and complete rest. The control curve was obtained two days previously under the same conditions.

acid intravenously. During the control day, the initial basal metabolic rate of −41 per cent dropped to −45 per cent in six hours, and rose to −40 per cent at the end of eight hours. On the treatment day the initial basal metabolic rate of −47 per cent rose to −35 per cent in six hours and dropped to −37 per cent at the end of eight hours. Although not a large increase, it seems significant.

The results in another case of myxedema are shown in Table 2. In this case there was a good deal of fluctuation during the control period (prob-

ably due to anxiety of the patient about fasting over this long period of time) and to some extent this vitiates the significance of the results obtained with triac and tetrac. After a single dose of 5 mg. of triiodothyroacetic acid there was a rise in the basal metabolism of about 20 points at the end of eight hours. At the end of twenty-four hours the basal metabolic rate had returned almost to the pretreatment level. Seven days later the experiment was repeated, using 10 mg. of triiodothyroacetic acid. Again there was a rise of about 10 points in the basal metabolic rate at the end of eight hours and a return to the pretreatment level in twenty-

TABLE 2. IMMEDIATE RESPONSE OF BASAL METABOLIC RATE TO SINGLE DOSES OF TRIIODOTHYROACETIC ACID, TETRAIODOTHYROACETIC ACID, AND *l*-THYROXINE IN A PATIENT WITH MYXEDEMA

	Hours after administration						
	0	2	4	6	8	9	24
Control	−26	−44	−53	−28	−31		−42
5 mg. triac	−42	−34	−32	−28	−22		−33
10 mg. triac	−32	−31	−26	−35	−23		−36
20 mg. tetrac	−40	−32	−36	−32	−32	−29	−33
40 mg. tetrac	−34	−34	−29	−27	−24	−23	−20
2.5 mg. *l*-thyroxine	−33	−33	−33	−31	−32	−29	−28

four hours. After an interval of a month, this patient received 20 mg. of tetraiodothyroacetic acid, which resulted in a rise of about 11 points (−40 to −29 per cent) in the basal metabolic rate at the end of nine hours. After another month the experiment was repeated with 40 mg. of tetraiodothyroacetic acid. The basal metabolic rate rose about 11 points (−34 to −23 per cent), rose a little further at the end of twenty-four hours, and stayed at a level of about −20 per cent for two weeks. There was a weight loss of almost 1 Kg. At the end of two months this patient received 2.5 mg. of *l*-thyroxine intravenously. The basal metabolic rate rose very little in the first twenty-four hours (−33 to −28 per cent) but by the sixth day was −6 per cent. The patient lost 2 Kg. in weight. The basal metabolic rate and weight returned to pretreatment levels in about two months. The constancy of the basal metabolism during the first nine hours after the injection of 2.5 mg. of *l*-thyroxine should be emphasized. This serves as a control for the responses to triac and tetrac. Thus, even if

the standard control period were discarded, the response to thyroxine was different from that to triac and tetrac.

It should be noted that after each injection there was little or no change in the level of blood cholesterol at the end of twenty-four hours. The concentration of blood cholesterol was not followed closely after the 5-mg. dose of triiodothyroacetic acid. After the 10-mg. dose there was a gradual drop of about 80 mg. per 100 ml. in two weeks, and a return to high values in another two weeks. After the 20-mg. dose of tetraiodothyroacetic acid there were equivocal changes after the first twenty-four hours. However, after the 40-mg. dose of tetraiodothyroacetic acid there was a drop of about 60 mg. per 100 ml. at the end of two weeks, and a return to the pretreatment level at the end of six weeks. After the intravenous injection of *l*-thyroxine, the cholesterol concentration did not change in the first twenty-four hours. There was a drop from 410 mg. to 356 mg. per 100 ml. at the end of one week, and return to 396 mg. per 100 ml. in two months.

The results in human myxedema substantiate the fact that triiodothyroacetic acid and tetraiodothyroacetic acid, during the first few hours after administration, induce a rise in basal metabolism which tends to subside at the end of twenty-four hours. This is in contrast to the relative lack of response to thyroxine in the first twenty-four hours.

DISCUSSION

In its effect on basal metabolism, tetraiodothyroacetic acid appears to be about one-fifteenth as active as *l*-thyroxine. It is difficult to compare the activity of triiodothyroacetic acid with that of thyroxine. From the data of Patient A. D., it would seem that a daily dose of 2.75 mg. elicited a response greater than that following a standard amount of 0.4 mg. of *l*-thyroxine. In the case of Patient B. W., the response during the first seven days of medication was near standard; the average dose during this period of treatment was 1.7 mg. daily. Consequently, the relative activity of triiodothyroacetic acid, when the dose is sufficient to elicit a response, is about a quarter to a sixth as great as that of *l*-thyroxine.

The rapid, transient effect induced by a single dose of 2 to 10 mg. of triiodothyroacetic acid intravenously, or by a single dose of 20 mg. of tetraiodothyroacetic acid intravenously, tends to confirm the findings of Thibault and Pitt-Rivers (4) on the action of these compounds. In rat kidney slice experiments they obtained an effect which was maximal in fifteen minutes and disappeared in ninety minutes. In thyroidectomized animals they obtained a rise in the basal metabolic rate within two hours; the effect wore off within four hours. The foregoing findings may explain the failure of the basal metabolic rate to increase appreciably in our study with daily doses of less than 1.5 mg. of triiodothyroacetic acid, inasmuch

as the material was usually administered in the afternoon and the basal metabolic rate obtained the following morning. At this dosage level, there is an apparent discrepancy between the metabolic effect and other effects of thyroid hormone in patients with myxedema. Over a two-week period, the serum cholesterol level dropped appreciably, the excretion of creatine in the urine rose considerably, the electrocardiographic pattern was reversed towards normal, there was a weight loss of 3 to 4 Kg., and there was definite improvement in the clinical picture. In contrast, the effect of thyroxine or triiodothyronine is cumulative at any dosage level with respect to the basal metabolic rate as well as with respect to other aspects of the myxedema response. We have no data on the effect of small doses of tetraiodothyroacetic acid and therefore do not know whether or not it elicits a dissociated response at a low-dosage level. Large doses of the acetic-acid analogues not only have an immediate effect on the basal metabolism, but also a prolonged effect; consequently large doses have the cumulative effect which is characteristic of thyroxine and triiodothyronine.

Since the lack of effect on the basal metabolic rate at low daily dosage levels of triiodothyroacetic acid is seen only when the material is administered in a single injection, it would be desirable to repeat the observation, giving the same amount of material in divided dosage. Trotter (7) administered triiodothyroacetic acid to 1 patient with myxedema every four hours for ten days and obtained an adequate basal metabolic response. However, his data are not comparable to those reported here, because the material was given orally and the total daily dosage was much larger (6 mg.). We have also given triiodothyroacetic acid orally to 1 patient with myxedema in divided dosage. After two weeks of daily dosage with 0.5 mg. and four weeks with 0.75 mg., the basal metabolic rate fluctuated one or two points around −30 per cent, whereas the blood cholesterol level dropped from 396 mg. to 286 mg. per 100 ml. It seems, therefore, that the dissociation in response is a function of dosage rather than of the route of administration.

On the basis of their data, Thibault and Pitt-Rivers suggested that the acetic-acid derivatives are the form in which the thyroid hormone acts in tissue. Their concept tends to be confirmed by certain of our observations in human myxedema—namely, the data in Table 2 and Figure 4, and also the lack of cumulative effect from triac at low dosage levels, which explains the dissociation of their effects on the basal metabolism compared with other aspects of myxedema. The observation reported by Roche *et al.* (8) working with kidney extract from hormone-treated animals, and by Albright *et al.* (9) working with mitochondria, that tissues convert thyroxine and triiodothyronine to their corresponding acetic-acid derivatives, lends further support to this theory.

That further degradation of the alanine side-chain does not play an important role in the action of thyroid hormone is attested by the fact that the formic-acid derivative of triiodothyronine, which is formed from the acetic-acid derivative by loss of one carbon atom, is inactive in human myxedema in dosage up to 20 mg. daily (10). At this dosage level the basal metabolic rate remained at −45 per cent, the blood cholesterol level, urinary creatine excretion and the electrocardiogram remained unchanged, although the serum protein-bound iodine level rose to 30 gamma per 100 ml.

The action of small doses of triiodothyroacetic acid in combatting the manifestations of myxedema without appreciably changing the basal metabolic rate, raised our hopes that this compound might be able to suppress the pituitary without affecting the basal metabolism. Ideally, such a compound would be useful in the treatment of hyperthyroidism. Our previous efforts in utilizing weak-acting thyroxine analogues (such as tetrabrom- and tetrachlorthyronine) in treating patients with hyperthyroidism (1), and those of Richards *et al.* (11) in treating animals, resulted in depression of thyroid function, but only in proportion to the increase in basal metabolism. We therefore administered triiodothyroacetic acid to a patient with hyperthyroidism in a dosage of 2 to 4 mg. daily intravenously. This dosage was chosen in order to avoid an "iodine effect." After 8 doses, the thyroidal radioactive iodine uptake dropped from 90 to 70 per cent and the basal metabolic rate from +54 to +41 per cent. Unfortunately, subsequent results were spoiled by technical errors which could not be corrected in time. Further observations along this line are in order.

SUMMARY AND CONCLUSION

Tetraiodothyroacetic acid, given intravenously, has a fifteenth the activity of *l*-thyroxine in raising the basal metabolic rate of patients with myxedema. In adequate dosage, triiodothyroacetic acid has a quarter to a sixth the activity of thyroxine.

Triiodothyroacetic acid in dosages under 1.5 mg. daily induces a dissociation of response in myxedema—the basal metabolic rate changes little, but there is the expected drop in the blood cholesterol level, an increase in the urinary excretion of creatine, a return of the electrocardiographic pattern to normal, appreciable loss of weight, and an improvement in the myxedematous appearance.

Large daily doses of the acetic-acid derivatives behave like thyroxine, in that they have a cumulative effect on the basal metabolism.

These findings in myxedema substantiate the fact that administration of triiodothyroacetic acid or tetraiodothyroacetic acid results in an ap-

preciable rise in the basal metabolism during the first few hours, which tends to subside at the end of twenty-four hours. In contrast, administration of thyroxine elicits little or no response during the first twenty-four hours. This favors the concept that the acetic-acid analogues are the form in which thyroid hormone acts in tissue.

The suggestion is made that these analogues may depress thyroid function in Graves' disease without raising the basal metabolism. Such studies are now in progress.

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STUDIES OF THE INHIBITORY EFFECT OF *l*-TRIIODOTHYRONINE ON THYROIDAL I^{131} UPTAKE IN EUTHYROID PERSONS AND PATIENTS WITH EXOPHTHALMIC GOITER*†

WILLIAM M. McCONAHEY, M.D. AND
CHARLES A. OWEN, JR., M.D.

Section of Medicine, and Section of Clinical Pathology, Mayo Clinic and Mayo Foundation,‡ Rochester, Minnesota

INHIBITION of thyroidal collection of I^{131} in human subjects by the oral administration of *l*-triiodothyronine has been studied by several groups of investigators. In euthyroid persons, Starr and Liebhold-Schueck (1, 2) compared the 24-hour uptake of I^{131} before the administration of *l*-triiodothyronine with the uptake after one week of administration of this substance. They reported that a daily dose of 8.8 micrograms resulted in maximal inhibition of uptake, whereas a dose of 4.4 micrograms was ineffective. Werner and Spooner (3) carried out similar studies in both euthyroid persons and patients with exophthalmic goiter, and found that a daily dose of 75 or 150 micrograms of *l*-triiodothyronine for eight days inhibited 24-hour uptake in euthyroid persons, but not in patients with exophthalmic goiter. These workers, as well as Perlmutter and Slater (4) have proposed this as a diagnostic test for exophthalmic goiter. In a group of 13 euthyroid control subjects, Starr and Liebhold-Schueck (1) compared the 24-hour thyroidal uptake of I^{131} before administration (23.4 per cent) with the 24-hour uptake after the daily administration of a placebo (lactose) for seven days (20.9 per cent), and thus found that the average difference between the two uptakes was 2.5 per cent, with a standard error of the mean of ± 7.

The technic employed in most of such studies to date has been to compare the collection of two tracer doses of I^{131}, one before and the other after administration of a certain daily dose of *l*-triiodothyronine for seven

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† The radioisotopes used in the studies reported in this paper were supplied by the United States Atomic Energy Commission.

‡ The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

to fourteen consecutive days. The present study was undertaken in order to evaluate the speed and degree of thyroid inhibition by observing the uptake of multiple small tracers at frequent (often daily) intervals in euthyroid and hyperthyroid persons given different daily doses of *l*-triiodothyronine for varying periods.

MATERIAL AND METHOD

Forty-four persons were studied, 37 of whom were normal individuals with no known thyroid abnormality and 7 of whom had exophthalmic goiter. First, the 24-hour thyroidal uptake of a small (usually 2 microcuries) I^{131} tracer was determined as a control measurement. Then *l*-triiodothyronine[1] was administered in a constant daily dosage for periods ranging from three to thirty-one days. These daily doses varied from 3.5 to 140 micrograms. During the period of administration of the hormone, 24-hour uptake was determined repeatedly by using small tracers of radioiodine, the total dose of I^{131} not exceeding 50 microcuries in any one person.

RESULTS

Figure 1 shows the 24-hour uptake of I^{131} in 5 euthyroid persons given small daily doses of *l*-triiodothyronine for periods ranging from nine to twelve days. It appears that inhibition of uptake did not occur in the person taking the 8.8-microgram dose, but that it did occur in the other 4

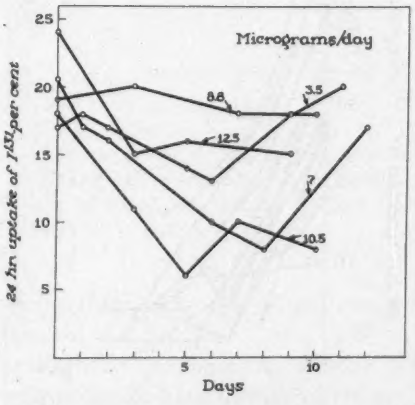

FIG. 1. Effect of oral administration of 3.5 to 12.5 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in euthyroid subjects.

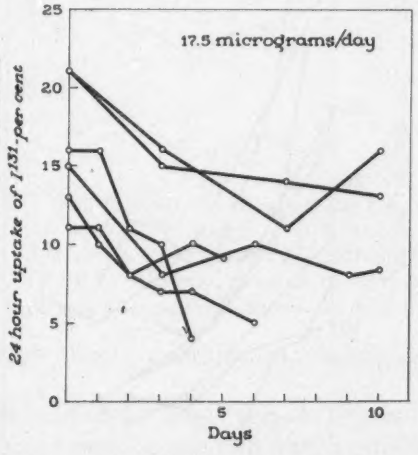

FIG. 2. Effect of oral administration of 17.5 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in euthyroid subjects.

[1] Kindly furnished by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

persons. In the 2 subjects taking doses of 3.5 and 7.0 micrograms respectively, the inhibition was temporary; by the sixth and eighth days respectively, the inhibitory effect of *l*-triiodothyronine had reached a maximum, but thereafter the 24-hour uptake of I^{131} increased toward or rose above the base-line level. In the 2 persons taking 10.5 and 12.5 micrograms per day, the inhibition of I^{131} uptake was moderate, but sustained, during the period of study.

Six euthyroid subjects received daily doses of 17.5 micrograms of *l*-triiodothyronine for periods ranging from four to ten days (Fig. 2). In all 6 persons, there was some inhibition of the 24-hour uptake of I^{131}, although variable in degree.

In all 8 subjects taking daily doses of 25 or 35 micrograms of *l*-tri-

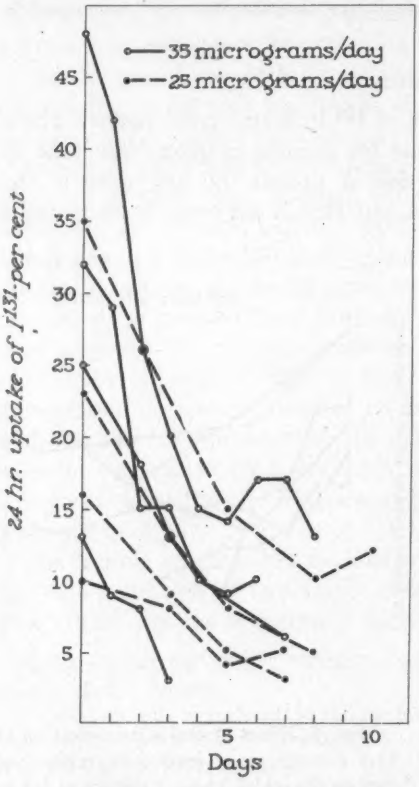

FIG. 3. Effect of oral administration of 25 and 35 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in euthyroid subjects.

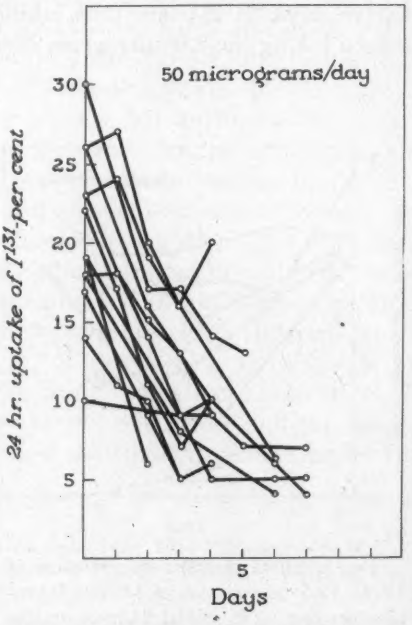

FIG. 4. Effect of oral administration of 50 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in euthyroid subjects.

iodothyronine for periods ranging from three to ten days there was a prompt and marked inhibition of I^{131} uptake by the thyroid (Fig. 3).

As seen in Figure 4, there was prompt inhibition of the 24-hour uptake of I^{131} in all 13 euthyroid subjects given 50 micrograms of *l*-triiodothyronine per day. In all subjects except 1, the 24-hour uptake had fallen to, or below 50 per cent of the control level by the second, third or fourth day of ingestion of the hormone.

In 2 persons given 70 micrograms and 3 persons given 140 micrograms of *l*-triiodothyronine per day (Fig. 5), the 24-hour uptake of I^{131} was de-

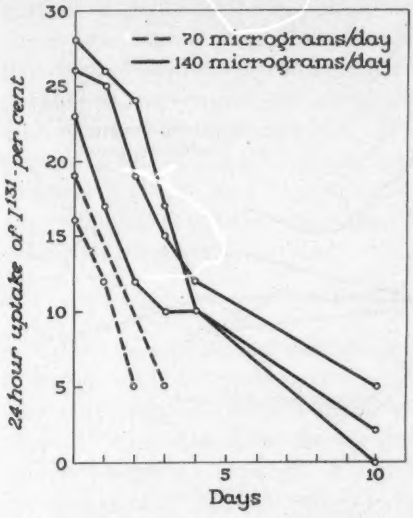

FIG. 5. Effect of oral administration of 70 and 140 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in euthyroid subjects.

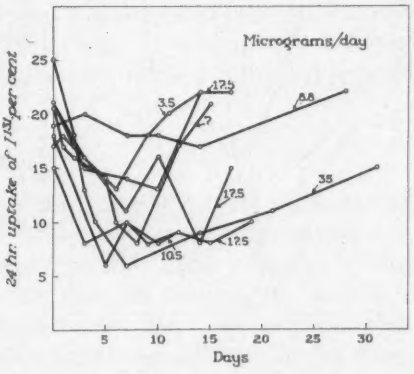

FIG. 6. Effect of oral administration of 3.5 to 17.5 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in euthyroid persons for periods ranging from twleve to thirty-one days.

creased by more than 50 per cent within three or four days of administration of the hormone.

Eight of the foregoing persons were studied for longer periods. Figure 6 shows the 24-hour uptake of I^{131} in these 8 persons who took varying doses of *l*-triiodothyronine for periods ranging from twelve to thirty-one days. There was no inhibition of uptake at any time in the subject who took 8.8 micrograms per day. In the subjects who took 3.5 and 7.0 micrograms per day and in 1 of those who took 17.5 micrograms per day, there was definite though transient inhibition of I^{131} uptake. Within nine to fourteen days after administration of *l*-triiodothyronine was started, the 24-hour

uptake of I^{131} in these 3 persons had returned to, or exceeded the control level. In the other 2 subjects receiving 17.5 micrograms and in the subject receiving 10.5 micrograms per day the inhibition was more lasting and persisted through periods of observation ranging from twelve to nineteen days. The initial 24-hour uptake of I^{131} in the subject who received a daily

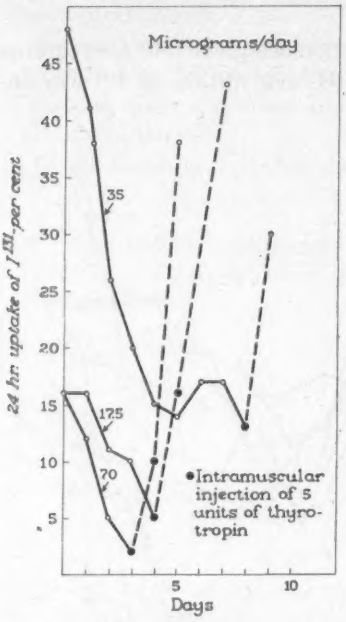

FIG. 7. Effect of intramuscular injection of thyrotropin into euthyroid subjects whose thyroidal 24-hour uptake of I^{131} had been inhibited by prior oral administration of daily doses of *l*-triiodothyronine. Administration of *l*-triiodothyronine was continued after injection of thyrotropin.

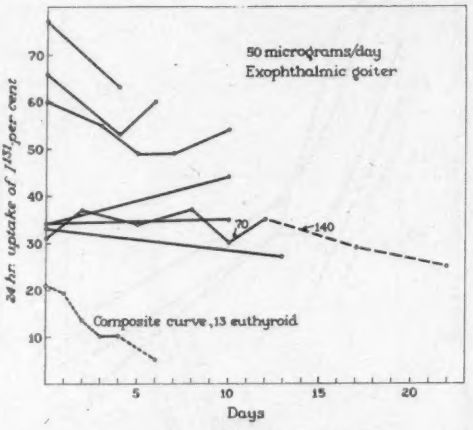

FIG. 8. Effect of oral administration of 50, 70 or 140 micrograms of *l*-triiodothyronine per day on thyroidal 24-hour uptake of I^{131} in patients with exophthalmic goiter.

dosage of 35 micrograms for thirty-one days was 25 per cent, but this quickly fell to a low of 6 per cent seven days after administration of *l*-triiodothyronine was begun. Then the 24-hour uptake began to increase gradually and by the thirty-first day it was up to 15 per cent.

In 3 euthyroid persons in whom the uptake of I^{131} had been markedly decreased by the previous administration of *l*-triiodothyronine, intra-

muscular injection of 5 units of thyrotropin[2] was followed by an increase in the 24-hour uptake of I^{131} toward, or in excess of the control level within twenty-four hours (Fig. 7).

The effect of *l*-triiodothyronine on 24-hour uptake of I^{131} was studied in 7 patients with exophthalmic goiter (Fig. 8). In 6 of these the daily dose was 50 micrograms, and in the seventh it was 70 micrograms for twelve days and 140 micrograms for the next ten days. Duration of treatment varied from four to twenty-two days. In 4 patients with the lowest uptakes, the administration of *l*-triiodothyronine caused no inhibition of the thyroidal collection of I^{131}. In the other 3 patients there was some suggestion of slight inhibition, since the slopes of the curves drawn through the points representing the 24-hour uptakes of I^{131} for the first four or five days of *l*-triiodothyronine administration in these 3 patients are comparable to the slope of the composite curve for the 13 euthyroid subjects who received 50 micrograms of *l*-triiodothyronine per day. However, the percentile fall of the I^{131} uptake in these 3 hyperthyroid patients was not impressive (18, 18 and 20 per cent, respectively) when compared with the percentile fall of uptake (more than 50 per cent) in most euthyroid persons taking 50 micrograms per day.

COMMENT

A daily dose of 25 to 140 micrograms of *l*-triiodothyronine administered to euthyroid individuals over a period of three to five days promptly and markedly reduced the proportion of a radioiodine tracer collected by the thyroid. When the daily dosage was less than 25 micrograms, the effect was inconsistent. Although 17.5 micrograms per day uniformly inhibited the uptake of I^{131} in the 6 subjects studied at this dosage level, in 4 of these subjects the inhibition did not reach 50 per cent in four to ten days of observation. When the daily dosage was 3.5 to 12.5 micrograms, there was transient inhibition of I^{131} uptake in 7 of 8 subjects; in the eighth subject a dose of 8.8 micrograms per day caused no significant decrease in the collection of I^{131}. It appears that the speed and degree of inhibition of I^{131} uptake induced by the administration of *l*-triiodothyronine are related to the size of the daily dose. With doses of less than 25 micrograms per day, inhibition appears more slowly and is less pronounced; with doses of more than 25 micrograms it is prompt and marked.

The observation that the intramuscular injection of 5 units of thyrotropin caused the I^{131} uptake which had previously been decreased by *l*-triiodothyronine ingestion to return to normal or above-normal levels

[2] The Armour Laboratories, Kankakee, Illinois.

would support the theory that *l*-triiodothyronine exerts its thyroid-suppressive action by the inhibition of secretion of thyrotropin.

SUMMARY

In daily doses of 3.5 to 17.5 micrograms, *l*-triiodothyronine administered to euthyroid subjects induced moderate, though often transient, inhibition of the 24-hour thyroidal uptake of I^{131} in most subjects. In daily doses of 25 to 140 micrograms it uniformly induced prompt inhibition of the 24-hour uptake; the larger the dose, the more rapid the inhibition.

The intramuscular injection of 5 units of thyrotropin was followed by the return to normal or above-normal levels of the 24-hour uptake of I^{131} previously decreased by ingestion of *l*-triiodothyronine.

There was no significant inhibition of the 24-hour thyroidal collection of I^{131} in 7 patients with exophthalmic goiter to whom *l*-triiodothyronine was administered.

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THYROID CANCER IN CHILDHOOD AND ADOLESCENCE*

JAMES D. MAJARAKIS, M.D., DANELY P. SLAUGHTER, M.D. AND WARREN H. COLE, M.D.

The Department of Surgery, University of Illinois College of Medicine and Illinois Research and Educational Hospitals, Chicago, Illinois

FIFTEEN cases of carcinoma of the thyroid gland in children and adolescents between 5 and 20 years of age were treated at the University of Illinois Research and Educational Hospitals from 1936 to 1956. Twenty years of age was chosen as the maximum in this study, since this is the time when the child has reached maturity and growth has ceased. Winship and Chase (1) compiled 285 cases from the literature up to 1955, but no definite maximum age was stated. Our Pathology Department, in accordance with the classification of Warren *et al.* (2), reported our series of 15 cases, of which 7 or 46.6 per cent were papillary adenocarcinoma, 5 or 33.3 per cent were adenocarcinoma, and 3 or 20.0 per cent were adenocarcinoma in adenoma (adenoma malignum).

Of the 15 patients, 9 were females and 6 males. The average duration of the mass in the thyroid or neck was 4.3 years. Our incidence of 31.1 per cent for carcinoma in nontoxic nodular goiter in children compares with that reported by others—Kennedy (3), 19.3 per cent; Hendrick *et al.* (4), 25.9 per cent; Ochsner *et al.* (5), 26.6 per cent; Ward (6), 40.0 per cent; and Winship *et al.* (1), 50.0 per cent. Preoperative diagnosis was made by us in 7 patients or 46.6 per cent; all had cervical node metastases. The diagnosis was made at operation in 3 cases or 20.0 per cent; 2 of these 3 patients had metastases in the neck. Diagnosis was made postoperatively in 33.3 per cent; none of these patients underwent radical neck operations, but 4 of the 5 received intensive irradiation.

THERAPY AND SURVIVAL

Since the incidence of carcinoma in nontoxic nodular goiter in children in our series was 31.1 per cent, we recommend total thyroidectomy on the involved side in nontoxic nodular goiter (as in adults), provided the opposite side is normal (7).

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This article will be included in the bound volume of the 1956 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available early in 1957.

In 6 cases of cancer in which the diagnosis was not made until the specimen was examined in the operating room (because the lesion was small and no nodes were palpable), total thyroidectomy without neck dissection was performed. Four of these patients were treated by maximum irradiation over the neck postoperatively, although no cervical nodes were removed or palpated; all are alive and apparently free of disease. One of them had an adenocarcinoma in an adenoma, diagnosed postoperatively by the pathologist; this patient is alive and free of palpable disease in the neck eighteen years after surgery. We have performed 9 thyroidectomies (usually total) combined with radical neck dissection (usually bilateral). In all of these patients we were able to identify metastatic disease in the adjacent cervical lymph nodes grossly, and to confirm it histologically. Winship and Chase (1) in a collective review of 285 cases of childhood thyroid carcinoma reported that 16.7 per cent died of their disease from nine months to twenty-three years after operation; 65 per cent of these tumors contained a papillary element. In our series, following 2 of 9 (22.2 per cent) thyroidectomies combined with radical neck dissection there was a recurrence in one and four years respectively. In both instances the lesion was papillary adenocarcinoma. Thus, in 2 of our 7 cases of papillary carcinoma there was recurrence following operation.

All 15 patients in our series are alive, but 22.2 per cent have residual disease. Some are receiving as much as 4 grains of desiccated thyroid daily, as recommended by Crile (8). Recurrence in this group having radical neck dissection is readily explainable. They had advanced cases of the disease, in contrast to the localized condition in the 6 patients not having neck dissection.

RELATIONSHIP OF PRIOR IRRADIATION TO THYROID CANCER

In 1950 Duffy and Fitzgerald (9) reported a series of 28 patients, 18 years or younger, with thyroid cancer; 10 of these received irradiation to the thymus gland between the fourth and sixteenth months of life. In 1955 Clark (10) reported that all of his 15 patients with thyroid cancer, aged 15 years or younger, had had x-ray therapy in infancy or early childhood for enlarged thymus, tonsils, pertussis or cervical adenitis. In our series we found that 10 of the 15 thyroid cancer patients had a history of having received irradiation to the head and neck between 2 months and 6 years of age (Table 1). The total dose administered varied from 200 to 625 r. Of the 15 patients, 5 were over 15 years of age at the time the diagnosis was made. None of these received prior irradiation, whereas all of the 10 children 15 years of age or younger with thyroid cancer had received prior irradiation in early infancy and childhood. Simpson *et al.* (11) in 1955 studied the frequency of neoplasia in 1,722 children who had re-

TABLE 1. HISTORY OF PRIOR IRRADIATION OF THE HEAD AND NECK IN 10 CASES* OF THYROID CANCER IN CHILDREN AND ADOLESCENTS TREATED AT THE ILLINOIS RESEARCH HOSPITALS 1936–1956

Age at which thyroid cancer diagnosed (yrs.)	Age at which prior irradiation given	Total dose of irradiation (r)
5	10 mos.	600
6	2 mos.	440
6	3 mos.	200
6	4 mos.	540
11	6 yrs.	440
12	4 yrs.	625
14	2 mos.	440
14	2 yrs.	200
14	6 yrs.	540
15	6 yrs.	280
Av. = 10.3	*Av.* = 2.6	*Av.* = 430

* This report concerns a total of 15 patients with thyroid cancer. Five did not receive prior irradiation to the head and neck; all of these were older than 15 years.

ceived x-ray therapy to the thymic area between the years 1926 and 1951. They reported 6 cases of thyroid cancer, 4 of carcinoma in other organs, and 8 cases of leukemia. This incidence in the treated group was markedly higher than that in either the untreated siblings or in the general population.

SUMMARY

Fifteen cases of thyroid cancer in children and adolescents between 5 and 20 years of age were observed during the period 1936–1956 at the University of Illinois Research and Educational Hospitals. Of these cancers, 46.6 per cent were papillary adenocarcinoma, 33.3 per cent were adenocarcinoma, and 20 per cent were adenocarcinoma in adenoma. Nine of the 15 patients were females. The average duration of the nodule in the neck or thyroid was 4.3 years. The incidence of carcinoma in nontoxic nodular goiter was 31.1 per cent. The diagnosis was made preoperatively in 46.6 per cent, at operation in 20.0 per cent, and postoperatively in 33.3 per cent.

In 6 of the 15 patients, no neck nodes were palpable and operation consisted of thyroidectomy alone; in 4 of these 6, x-ray therapy was also given. In 9 patients with obvious metastases to the neck nodes, radical neck dissection was performed in addition to the thyroidectomy. All 15

are alive, but 2 of 9 patients who underwent radical neck dissection have a recurrence. In these 2 instances, papillary adenocarcinoma recurred one and four years respectively after operation. The longest survival time has been eighteen years. Of the entire series 53.3 per cent are alive from one to ten years after operation, and 46.6 per cent are alive ten or more years after operation.

Of the 10 patients 15 years of age or younger, all had had x-ray therapy to the head and neck in infancy or childhood; the dosage varied from 200 to 625 r. None of the patients between the ages of 16 and 20 had had irradiation.

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EFFECT OF DIETHYLSTILBESTROL ON THE BINDING OF THYROXINE IN SERUM*†

J. THOMAS DOWLING, M.D.,‡ NORBERT FREINKEL, M.D. AND SIDNEY H. INGBAR, M.D.

The Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, the Department of Medicine, Harvard Medical School, Boston, Massachusetts, and the Howard Hughes Medical Institute

AN APPARENT paradox in thyroidal economy is presented by the normally pregnant woman. Thus, there occurs during pregnancy thyroidal hyperplasia, augmentation of the thyroidal accumulation of radioiodine, and an increase in the concentration of circulating thyroid hormone (1–5). These changes, ordinarily associated with the thyrotoxic state, are not accompanied during pregancy by symptomatic stigmata of thyrotoxicity nor by increases in basal oxygen consumption beyond those which have been attributed to fetal needs (6).

Recently, in an effort to investigate this unique dissociation, studies have been made of the manner in which thyroxine is partitioned among the various proteins in the serum of pregnant women compared with that of controls (7, 8). These studies revealed a marked augmentation during normal pregnancy in the thyroxine-binding capacity of that α-globulin moiety of serum which has been termed the thyroxine binding protein (TBP). This augmentation begins early in pregnancy, persists throughout the gravid period, and gradually disappears during the puerperium. Moreover, a large proportion of women with threatened or inevitable abortion fail to demonstrate the usual gravid change in thyroxine-binding by TBP.

The origin of the gravid alteration in the thyroxine-binding capacity of TBP is unknown. However, several observations suggest that profound

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‡ Fellow in Cancer Research of the American Cancer Society.

changes in the metabolism of estrogens which occur during pregnancy might be contributory. During both the gravid and the postpartum periods, alterations in the level of serum protein-bound iodine and in thyroxine-binding by TBP are qualitatively similar and temporally coincident (7, 8). Furthermore, it has been demonstrated that large doses of estrogen, when administered to males or to nonpregnant females, induce increases in the serum PBI level comparable to those which occur during normal pregnancy (9, 10). Finally, a profound and progressive increase in the elaboration of estrogen is a concomitant of normal pregnancy (11). For these reasons, studies have been made of the effect of estrogen on the thyroxine-binding capacity of TBP in the plasma of a variety of nonpregnant patients. This hormonal regimen has induced augmentations of thyroxine-binding by TBP which are, by the techniques employed, entirely comparable to those which occur during normal pregnancy.

MATERIAL AND METHODS

Included in the study group of 16 patients were 7 apparently euthyroid individuals (4 postmenopausal females, 2 hypogonadal males, and one 38-year-old woman (P.B.) with idiopathic hirsutism and normal menses), 4 patients with primary myxedema, 4 patients with panhypopituitarism, and 1 young woman with hyperthyroidism only partially controlled by large doses of propylthiouracil (1,000 mg. daily). Patients with primary myxedema received their usual daily maintenance dose of exogenous thyroid hormone (2 grains of desiccated thyroid or 0.1 mg. of *l*-thyroxine sodium) throughout the study. Three of the 4 hypopituitary patients received daily maintenance doses of desiccated thyroid (2 to 3 grains) and cortisone (25 mg.). One patient (C.A.) with intrasellar tumor, who displayed gonadal and adrenal but no thyroidal insufficiency was treated with cortisone only (25 mg. daily). Except in the case of the thyrotoxic patient, all patients were clinically eumetabolic, and their control basal metabolic rates (BMR) and serum protein-bound iodine (PBI) levels were within normal limits.

All subjects received diethylstilbestrol in daily oral doses of 30 mg. for periods ranging from four to eight weeks. The thyrotoxic patient received 30 mg. daily for five weeks and 60 mg. daily during the ensuing five weeks. One patient with treated myxedema (B. K.) received 30 mg. daily for four weeks and has received 60 mg. daily since then up to the time of preparation of this manuscript. One patient with panhypopituitarism (R.R.) received 30 mg. of diethylstilbestrol daily for five weeks, followed by stilbestrol plus 75 mg. of buccal progesterone for two weeks, then progesterone alone for four weeks.

Measurements of thyroidal accumulation of I^{131}, BMR, serum PBI level, and thyroxine-binding capacity of TBP were made at intervals prior to, during, and following administration of estrogen. Details of timing and the dosages of estrogen are presented in Table 1.

In studying the thyroxine-binding capacity of TBP in sera, the following procedure was employed. A 30-ml. sample of antecubital venous blood was obtained without stasis and allowed to clot. Following syneresis, concentrations of total protein and of albumin were determined in the separated sera, the former by a modified biuret method (12) and the latter by the anionic dye adsorption method of Rutstein, Ingenito and Reynolds (13). Aliquots of serum were analyzed for PBI by the method of Barker (14). The remaining serum was stored in the frozen state pending completion of the study.

TABLE 1. THE INFLUENCE OF DIETHYLSTILBESTROL ON THYROXINE-BINDING BY TBP AND ON VARIOUS INDICES OF THYROIDAL ECONOMY

Subject, sex and age	Period	Duration of period (wks.)	BMR (%)	Thyroidal I^{131} uptake (% dose)	Serum PBI (μg./100 ml.)	Serum tot. protein (Gm./100 ml.)	Serum albumin (Gm./100 ml.)	Per cent of added thyroxine bound to TPB or albumin							
								Thyroxine added per 100 ml. serum*							
								10 μg.		48 μg.		85 μg.		160 μg.	
								TBP†	A‡	TBP	A	TBP	A	TBP	A
Euthyroid															
1.	Control	0	−4	30.6	7.2	7.5	4.0	83.8	10.2	46.6	40.4	37.6	48.1	31.3	55.5
M.T.	Diethylstilbestrol, 30 mg.	1		33.5	7.5	7.4	3.8	81.0	11.2	53.0	30.0	38.1	41.1	27.5	54.1
F		2			8.0	7.1	3.6	87.3	6.6	66.8	25.5	46.0	39.7	40.2	46.2
58		4	−20	32.2	8.6	7.1	3.7	84.5	7.0	67.2	25.0	46.5	39.6	39.3	47.9
	Control	1	−14		7.7	7.3	3.8	80.4	12.3	53.1	36.9	42.5	46.0	31.2	57.3
		2			6.4	7.3	3.7	81.6	10.5	51.6	35.8	39.1	45.6	26.4	56.5
		5	−10		7.0	7.4	3.9	80.2	16.2	44.7	42.6	34.7	53.5	27.9	57.3
2.	Control	0	−4	27.2	7.7	7.2	4.2	88.3	7.8	52.3	34.9	39.9	43.1	32.3	52.3
E.R.	Diethylstilbestrol, 30 mg.	2			9.3	7.1	3.4	87.7	6.8	71.4	18.8	52.5	34.7	41.8	42.9
F		4	−18		10.7	6.9	3.5	90.7	4.8	79.4	11.1	60.1	28.5	44.9	41.2
67		7	−19	26.0	10.1	6.7	3.4	89.4	6.3	76.7	12.7	57.9	27.5	45.4	42.6
	Control	2	−19		7.4	7.1	3.5	89.6	6.0	76.1	13.3	55.5	31.0	41.8	41.0
3.	Control	0	−3		7.4	7.3	3.5	82.3	13.8	43.5	48.4	32.9	57.3	25.9	63.0
M.MacK.	Diethylstilbestrol, 30 mg.	2			8.3	7.9	3.5	86.1	8.3	78.1	13.8	63.2	27.0	39.4	40.8
F		4	0												
54		6			9.3	7.9	3.4	87.4	6.5	82.4	11.6	67.9	21.7	45.7	40.3
		8	+3		9.1	8.4	3.5	87.8	6.5	82.4	11.6	60.3	26.0	48.1	38.0
	Control	2	0		8.3	8.4	—	85.4	8.5	75.8	18.9	54.1	36.1	38.2	50.1
		4			7.8	8.2	3.7	82.4	10.1	62.7	31.0	46.1	46.0	32.1	60.6
		9	−7												
4.	Control	0			6.0	6.4	3.6	75.0	15.0	43.2	42.3	29.5	49.5	23.7	61.3
P.B.	Diethylstilbestrol, 30 mg.	5			5.7	7.2	3.5	87.1	8.8	70.6	17.5	51.7	33.8	39.2	46.6
F															
38	Control	4			4.4	6.6	3.6	83.2	9.5	56.6	32.4	39.9	47.4	32.3	53.0
5.	Pre-orchiectomy	0			7.4	6.6	3.0	85.7	9.7	51.5	39.3	38.3	51.9	30.3	61.7
M.G.	Post-orchiectomy	0	+12	40.3		7.5	3.2	87.2	8.0	56.3	38.3	36.2	52.7	25.7	63.1
M															
71	Diethylstilbestrol, 30 mg.	8		38.4	9.7	6.2	3.0	88.1	7.0	75.1	16.8	56.5	36.1	38.1	51.0
6.	Control	0	−3	40.7	6.4	6.3	3.5	79.4	15.8	42.2	47.1	31.0	56.9	20.8	67.7
R.C.	Diethylstilbestrol, 30 mg.	7	−3	40.9	10.5	6.7	3.5	87.5	8.0	66.1	22.8	52.6	35.8	38.2	48.4
M															
26	Control	4						84.6	11.8	40.5	44.5	32.5	52.4	24.8	60.4
		8			4.4										

TABLE 1—(*continued*)

Subject, sex and age	Period	Duration of period (wks.)	BMR (%)	Thyroidal I^{131} uptake (% dose)	Serum PBI (μg./100 ml.)	Serum tot. protein (Gm./100 ml.)	Serum albumin (Gm./100 ml.)	Per cent of added thyroxine bound to TBP or albumin							
								Thyroxine added per 100 ml. serum*							
								10 μg.		48 μg.		85 μg.		160 μg.	
								TBP†	A‡	TBP	A	TBP	A	TBP	A
7.	Control	0	+5	20.0	4.6	6.6	3.8	80.9	10.4	48.7	41.3	33.4	52.5	27.2	55.4
V.C.	Diethylstilbestrol, 30 mg.	3			5.2	6.9	3.7	91.9	4.5	76.3	15.8	50.5	37.8	37.1	47.2
F		4	−16		4.7	7.1	3.2	86.6	6.3	75.1	15.3	54.8	34.8	40.8	41.1
54		5		20.6	5.5	6.7	3.8	84.3	6.7	75.8	16.6	55.3	28.2	40.8	41.7
		6	−16		4.8	6.2	3.7	91.4	5.5	71.1	23.4	53.9	37.4	40.4	46.1
	Control	2			5.0			87.1	7.4	66.9	25.5	44.7	45.0	31.7	55.6
		4	−24			7.0	3.9	83.2	11.0	53.5	39.0	37.9	54.5	26.0	66.4
		6	−17		4.5			83.3	11.8	47.0	46.5	33.3	59.2	28.2	62.1
		10			4.7										
Myxedema, treated															
8.	Control	0	+14		5.5	7.9	3.9	77.4	15.6	39.0	53.4	31.3	59.4	22.4	68.4
K.M.	Diethylstilbestrol, 30 mg.	3	+3		6.2	7.0	3.7	86.2	9.5	75.2	20.1	49.7	42.1	33.3	52.5
F		7	+3		5.2	7.1	3.4	88.5	7.4	80.5	15.2	58.3	34.7	36.0	52.0
55	Control	2			5.6	7.1	4.0	84.7	10.2	77.7	21.3	54.3	37.5	37.1	53.4
		4	+7			7.6	4.2	87.8	7.3	70.3	23.9	52.0	40.5	34.8	56.4
		6	−3			7.6	4.2	85.0	6.1	55.0	39.4	40.4	54.4	26.3	68.6
		10	+7												
9.	Control	0	−1		3.1	6.9	4.1	82.0	11.5	54.0	36.2	37.4	46.9	25.7	57.4
M.M.															
F	Diethylstilbestrol, 30 mg.	5	−3		3.2	7.0	3.9	85.0	9.3	76.7	15.6	56.8	32.9	36.5	48.5
61															
10.	Control	0	+5		4.6	6.9	3.7	81.3	12.1	56.5	34.6	44.8	43.7	31.1	55.9
		0	−1		4.8	6.9	3.8	84.1	10.0	57.6	32.9	44.5	46.0	35.0	57.0
B.K.	Diethylstilbestrol, 30 mg.	2			6.5	6.6	3.6	86.9	7.7	83.8	9.3	62.6	28.1	42.4	42.5
F		4	−3		6.7	6.4	4.6	88.3	7.4	81.9	11.6	60.7	30.0	43.5	39.2
62	Diethylstilbestrol, 60 mg.	4	+9												
11.	Control	0	+11		6.5	7.9	4.0								
M.McK.	Diethylstilbestrol, 30 mg.	2	−2		5.4	8.0	4.6								
F		5	−13		5.5	7.6	3.6								
56		8	−15		5.7	7.7	4.0								
	Control	2	−27		6.8	7.9	4.2								
		4	−9		6.6	7.6	4.4								

TABLE 1—(*continued*)

Subject, sex and age	Period	Duration of period (wks.)	BMR (%)	Thyroidal I^{131} uptake (% dose)	Serum PBI (μg./100 ml.)	Serum tot. protein (Gm./100 ml.)	Serum albumin (Gm./100 ml.)	Per cent of added thyroxine bound to TBP or albumin							
								Thyroxine added per 100 ml. serum*							
								10 μg.		48 μg.		85 μg.		160 μg.	
								TBP†	A‡	TBP	A	TBP	A	TBP	A
Hypopituitarism, treated															
12.	Control	0	+3		3.6	7.3	4.1	91.2	6.1	55.9	37.8	38.8	50.4	23.6	65.7
R.R.	Diethylstilbestrol, 30 mg.	2						90.8	5.4	80.3	7.8	66.0	25.1	49.0	31.6
M		5			4.4	6.9	4.0	86.7	2.7	82.6	3.4	67.9	17.9	58.6	28.7
62	Diethylstilbestrol, 30 mg.	2	−18			6.8	4.1	80.7	6.5	67.5	18.5	54.7	32.7	45.4	43.4
	Progesterone, 75 mg.														
	Progesterone, 75 mg.	2			2.8	6.9	3.7	80.5	5.1	58.1	24.7	50.2	34.1	43.1	48.8
		4			2.9			86.2	6.3	56.0	40.3	35.6	60.8	25.5	71.7
	Control	2	−34		3.1	7.1	3.9	86.9	6.8	53.8	41.7	34.5	59.6	32.2	72.1
		3						86.6	8.5	52.9	42.7	40.3	56.2	24.6	71.7
13.	Control	0	+15	33.5	4.1	6.7	3.3	81.3	10.8	60.3	26.7	47.4	40.1	33.1	52.1
C.A.	Diethylstilbestrol, 30 mg.	5	+11	29.8	4.9	6.7	3.2	84.6	8.9	74.9	15.5	57.4	33.3	39.0	44.6
M	Control	2						85.9	9.6	78.5	15.8	59.7	34.7	37.3	49.4
68		6			4.8	7.0	3.9	80.1	12.6	54.6	37.1	39.6	50.5	28.4	60.0
14.	Control	0		12.4		6.4	2.9	87.1	11.1	58.2	32.2	46.2	43.8	37.7	55.3
		0	−10		4.3	6.3	3.0	82.1	11.9	46.8	45.1	35.4	57.1	30.9	60.7
J.R.															
M	Diethylstilbestrol, 30 mg.	1				5.7	3.0	86.4	11.1	58.3	35.6	42.9	52.1	30.2	63.7
83		5		5.4		7.1	2.7	89.1	9.5	77.8	17.5	57.1	36.2	40.6	52.8
15.	Control	0	+6		4.5	7.9	3.3	79.6	10.6	43.7	44.4	35.5	46.7	33.8	58.9
M.B.															
F	Diethylstilbestrol, 30 mg.	5			4.9	6.7	3.2	87.3	4.5	76.8	16.5	55.8	33.7	31.8	54.1
54		8	0		5.8	7.3	3.3	89.9	9.5	75.2	19.4	50.6	34.1	36.0	50.1
Hyperthyroidism, partly controlled with propylthiouracil															
16.	Control	0	+32		10.2	6.4	3.4	72.5	15.0	43.0	39.7	29.4	55.4	27.3	56.9
G.W.	Diethylstilbestrol, 30 mg.	5	+39		10.2	6.3	3.5	73.7	13.5	45.0	38.4	30.0	54.9	26.4	53.1
F	Diethylstilbestrol, 60 mg.	3	+39		12.9	6.3	3.5	73.4	15.4	40.4	45.0	29.5	50.0	23.9	60.5
22		5	+37		11.3	5.9	3.5	70.9	19.5	41.9	44.7	30.3	54.1	22.5	62.7
		7	+41					71.5	18.5	43.5	44.0	32.2	51.2	27.8	53.7

* Based on gravimetric addition.
† Percentage of added radiothyroxine migrating in zone of thyroxine-binding protein.
‡ Percentage of added radiothyroxine migrating with albumin.

Concurrent analyses of the thyroxine-binding capacity of TBP in all the sera obtained were performed by techniques previously described, utilizing zone-electrophoresis of aliquots of sera enriched to four standard concentrations of added labelled and unlabelled thyroxine, and employing an automatically recording strip-scanner for analysis of the distribution of radioactivity in the resulting electrophoretograms (8). All sera from individual subjects were intercompared in a single electrophoretic analysis providing 32 individual electrophoretograms, in duplicate, daily. Electrophoreses were performed in two periods of six days, using the same stock solution of stable thyroxine in 1 per cent albumin, and two different fresh lots of labelled thyroxine adjusted to the same concentration in each of the two periods. In addition, sera from 4 nonpregnant women, 3 males, and from 5 pregnant women at term were analyzed together with the other samples during each six-day period.

Following assessment of the percentile partition of radioactivity between albumin and TBP, obtained from the scanning patterns of the representative electrophoretograms, duplicates of the latter were stained for proteins by the method of Durrum (15) and the distribution of the electrophoretic components was analyzed by photoelectric densitometry.

RESULTS

Data obtained in individual patients are presented in Table 1. In addition, Table 2 summarizes findings in the various clinical categories studied, as well as data concerning the binding of thyroxine by TBP in concurrently assayed sera of 5 pregnant women and of control subjects (4 women and 3 men with normal gonadal function). Table 3 summarizes the statistical significance of the various findings. The findings in Patient G. W., although presented in Table 1, are not included in group calculations, since this severely thyrotoxic patient demonstrated no symptomatic or physical evidence of estrogenic effect during the administration of diethylstilbestrol. All statistical analyses were performed according to methods by Snedecor (16).

TABLE 2. THYROXINE-BINDING BY TBP IN SERA OF NORMAL PATIENTS AND OF PATIENTS IN THE POSTMENOPAUSAL, HYPOPITUITARY, AND/OR PREGNANT STATE

Category	No. of patients	TBP*			
		Thyroxine added per 100 ml. serum†			
		10.0 μg.	48.0 μg.	85.0 μg.	160.0 μg.
Control	7	75.5±2.5	42.5±4.0	28.9±2.7	23.8±2.0
Post-menopause	4	83.8±2.7‡	47.8±3.7‡	35.9±3.4‡	29.2±3.1‡
Hypopituitarism	4	84.8±5.3‡	54.5±9.4‡	42.0±5.8‡	34.6±9.9
Normal pregnancy	5	91.1±1.0‡	81.5±5.1‡	59.9±6.1‡	38.1±4.3‡

* Percentage of radiothyroxine migrating with TBP. Value presented is mean ± std. deviation.

† Based on gravimetric addition.

‡ Values significantly different from comparable control (P = .05 or less).

TABLE 3. DIETHYLSTILBESTROL-INDUCED ALTERATIONS IN THYROXINE-BINDING BY TBP: STATISTICAL SIGNIFICANCE OF INDIVIDUAL AND GROUP DIFFERENCES

Category	No. of patients	TBP* Thyroxine added per 100 ml. serum† 10.0 μg. M‡	P value	48.0 μg. M	P value	85.0 μg. M	P value	160.0 μg. M	P value
Paired values in individual patients									
Control vs. 2 wks. Rx.	5	+1.8	—§	+24.9	.001	+19.3	.001	+12.9	.02
Control vs. 5 wks. Rx.	7	+4.6	—	+27.0	.001	+21.4	.001	+11.2	.02
Control vs. 7–8 wks. Rx.	6	+7.8	.001	+29.9	.001	+21.6	.001	+13.5	.001
2–3 wks. Rx. vs. 7–8 wks. Rx.	7	−0.3	—	+ 1.5	—	+ 1.2	—	+ 4.0	.05
Control vs. off Rx. 2 wks.	6	+3.4	—	+22.7	.001	+14.2	.001	+ 6.6	—
Control vs. off Rx. 4–5 wks.	6	+3.8	—	+11.5	—	+ 7.9	—	+ 4.4	—
Last week Rx. vs. 2 wks. off	6	−2.0	—	− 4.4	—	− 4.7	.05	− 6.0	.05
Last week Rx. vs. 4–5 wks. off	6	−4.2	.001	−18.3	.001	−13.4	.001	−10.6	.001
Group comparisons									
2 wks. Rx. vs. normal pregnancy	5vs.5	+3.3	.01	+ 5.4	—	+ 1.8	—	− 4.5	—
5 wks. Rx. vs. normal pregnancy	7vs.5	+4.8	.001	+ 5.0	—	+ 2.5	—	− 2.8	—
7–8 wks. Rx. vs. normal pregnancy	6vs.5	+2.6	.001	+ 5.5	—	+ 3.9	—	− 2.2	—

* Percentage of radiothyroxine migrating with TBP.
† Based on gravimetric addition.
‡ Mean difference; second category minus first.
§ Not significantly different ($P > .05$).

Thyroxine-binding protein

In confirmation of earlier findings (7, 8), a marked augmentation was noted in the percentage of thyroxine bound to TBP in the sera of pregnant women as compared to those of controls. This occurred at all four concentrations of added thyroxine. The 4 postmenopausal females, as well as the 4 patients with hypopituitarism also displayed control values of thyroxine-binding by TBP which, at three of four concentrations of added thyroxine, were significantly greater than those found in concurrently assayed sera from controls, but significantly less than values in sera from pregnant women.

Except in the 1 patient with active Graves' disease, administration of diethylstilbestrol was associated in all patients with an increase in the percentage of added thyroxine bound to TBP. According to the "paired *t* test," a significant increase in TBP activity was noted in patients treated for two weeks, which persisted thereafter while the hormonal regimen was unaltered. In only 1 patient (R.R.) did TBP activity decrease during

continued administration of diethylstilbestrol, and in this instance, 75 mg. of buccal progesterone daily had been added to the regimen. In 7 patients whose thyroxine-binding was assayed during the second or third week of therapy and again during the fourth to eighth week, no significant further increase in the percentage of thyroxine bound to TBP could be discerned, except at the highest concentration of added thyroxine employed.

In patients treated for two weeks, values for thyroxine-binding by TBP had increased to levels not significantly smaller than those found during

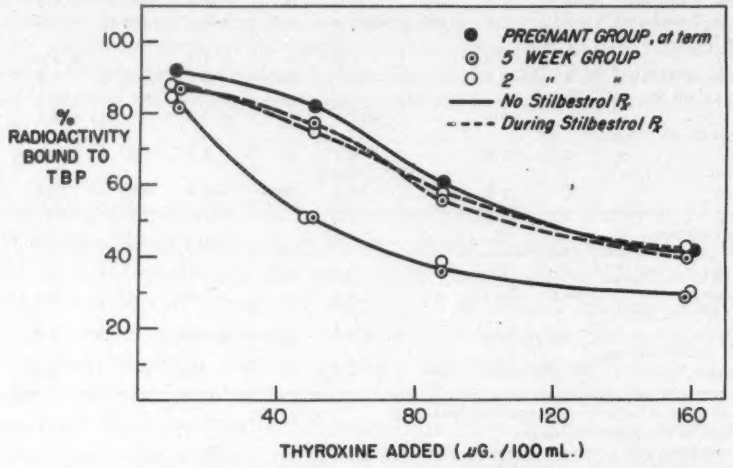

FIG. 1. The effect of diethylstilbestrol on thyroxine-binding by TBP. Alterations in thyroxine-binding induced by estrogen are compared with those found during normal pregnancy.

normal pregnancy, except at the lowest concentration of thyroxine employed. Similar findings were noted in the groups treated for five weeks and for seven to eight weeks.

Following withdrawal of diethylstilbestrol, the percentage of added thyroxine bound by TBP declined slowly toward normal. Comparison of thyroxine-binding by TBP in the serum obtained from 6 patients just prior to, and again two weeks after cessation of therapy revealed a significant diminution only at the two highest concentrations of thyroxine. By four to five weeks after treatment was discontinued, however, a highly significant diminution had occurred at all concentrations of added thyroxine, and values were no longer significantly greater than those present in the same patients prior to the exhibition of estrogen. In Patient R. R., a decline in thyroxine-binding by TBP was noted, despite continuance of

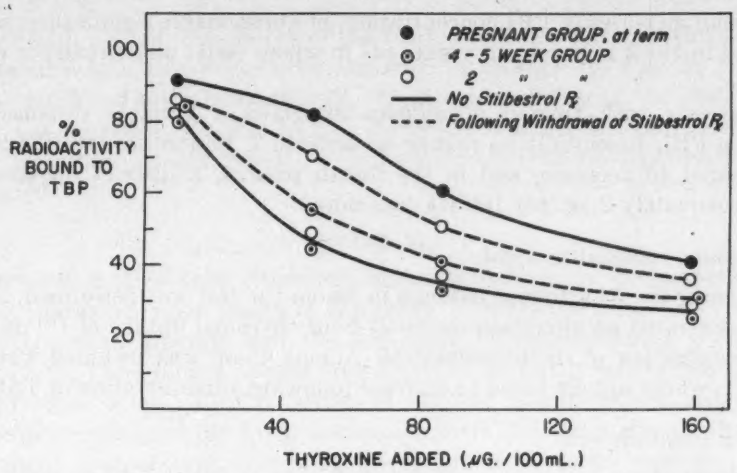

FIG. 2. Restoration toward normal of augmented thyroxine-binding by TBP following withdrawal of diethylstilbestrol. Values at two and four weeks following cessation of estrogenic therapy are compared with those found in the same patients prior to the administration of hormone, and with those found during normal pregnancy.

diethylstilbestrol, when 75 mg. of buccal progesterone daily was added to the regimen. Continuance of the latter hormone did not prevent the return of thyroxine-binding to normal when diethylstilbestrol was withdrawn.

Total protein and albumin

Consistent and significant changes in the total protein or albumin concentrations of serum did not occur during administration of diethylstilbestrol.

Protein-bound iodine (PBI)

Administration of diethylstilbestrol was associated with augmentation of the serum PBI level in 5 of 7 patients with presumably intact thyropituitary axes. For the entire group, the increase in PBI concentration averaged 1.8 μg. per 100 ml. and was statistically significant according to the paired *t* test. Among those patients whose PBI level failed to increase under estrogenic therapy, 1 (V.C.) was of particular interest. She was a 54-year-old woman with Hashimoto's struma, proved by thyroidal biopsy. Subsequent to withdrawal of diethylstilbestrol, she demonstrated no increase in thyroidal uptake of radioiodine or in serum PBI concentration following the administration of 5 units of thyroid-stimulating hormone (TSH). At the time of writing, the other patient whose PBI failed to increase (P.B.) has not been available for comparable testing.

Small increases in PBI concentration, of questionable significance, were noted in the 3 hypopituitary patients in whom serial measurements were made.

Patients with treated myxedema displayed a variable response of serum PBI. Essentially no change occurred in 2. In another the PBI level appeared to decrease, and in the fourth patient, a distinct increase of approximately 2 μg. per 100 ml. was noted.

Thyroidal radioiodine uptake

Among the 5 euthyroid patients in whom the test was performed, none demonstrated an alteration in the 24-hour thyroidal uptake of I^{131} during administration of diethylstilbestrol. Among these was included Patient V. C., whose uptake failed to increase following administration of TSH.

Basal metabolic rate

Despite frequent augmentations of the serum PBI level, significant increases in BMR were not noted during estrogenic therapy. In 3 of 5 euthyroid subjects, the BMR decreased by at least 15 per cent of normal. For the entire group, however, statistically significant diminution could not be detected. Decreases in BMR of 10 per cent of normal or more were noted in 2 patients with treated myxedema and in 1 with hypopituitarism. Although changes in BMR of the myxedematous-hypopituitary group were statistically significant, interpretation of the findings is made difficult by failure of the BMR to return to control values following cessation of therapy.

Symptomatic effects

Estrogenic effects were noted in all patients except G. W., a young woman with poorly controlled thyrotoxicosis, in whom diethylstilbestrol was administered in dosages as large as 60 mg. daily. Among the effects noted were increased areolar pigmentation, swelling and tenderness of the breasts in both males and females, and withdrawal uterine bleeding in the latter. A gain in weight of 3 to 5 pounds was common during the first week of administration and either persisted without increase or slowly subsided during the remainder of the period of estrogenic therapy. Evidences of estrogenic effect regressed promptly following withdrawal of diethylstilbestrol.

Findings perhaps related to alterations in thyroidal economy were noted in several patients. In Patient B. K. with treated myxedema a distinct delay developed in the relaxation phase of the deep tendon reflexes. During administration of estrogen, Patient M. McC. complained of drying of the skin and hair, intolerance to cold, and constipation, to-

gether with delay in relaxation of the tendon reflexes. These findings disappeared within two weeks after cessation of therapy. In Patient V. C. there developed intolerance to cold, constipation, drying of the skin and hair, but no reflex changes. In this subject, the BMR has continued to decrease following withdrawal of diethylstilbestrol, and symptoms have persisted.

DISCUSSION

Previous studies have demonstrated an alteration in the manner in which thyroxine, when added to the serum of pregnant women, is partitioned between albumin and the α-globulin thyroxine-binding protein, TBP (7, 8). Thus, during normal pregnancy, an unusually large percentage of thyroxine when added to serum in varying concentrations migrates electrophoretically at pH 8.6 in association with TBP. This change during pregnancy is associated with other alterations in thyroidal economy, including thyroidal hyperplasia, increased thyroidal avidity for iodine and an increase in the circulating concentration of protein-precipitable, butanol-extractable iodine (4, 17, 18).

In view of the profound change in the metabolism of estrogens which occurs during pregnancy, initial efforts to elucidate the origin of the gravid alteration in thyroxine-binding in serum have been directed toward evaluating the effects of large doses of estrogenic materials on thyroxine-binding by TBP. Diethylstilbestrol was chosen because of its ease of administration to non-hospitalized patients, and because of its previously demonstrated capacity to induce augmentations in the serum PBI level (9, 10). In all eumetabolic patients, alterations in thyroxine-binding by TBP comparable to those occurring during normal pregnancy were induced by this synthetic estrogen in a dosage of 30 mg. daily. That this response is not dependent on intact thyroidal or anterior hypophyseal function is indicated by the observation that equivalent degrees of change in thyroxine-binding were achieved in postmenopausal women, hypogonadal men, and in patients with primary myxedema or hypopituitarism.

No response in TBP was noted in Patient G. W., a 23-year-old woman with incompletely controlled thyrotoxicosis. This patient, in contrast to all others, displayed no evidence of estrogenic effects, even when the dosage of diethylstilbestrol was increased to 60 mg. daily. A more rapid utilization of adrenal corticosteroids, and decreased sensitivity thereto, has been demonstrated in patients with thyrotoxicosis (19, 20). It appears possible that previously observed resistance of thyrotoxic animals to estrogenic stimulation (21), to which the observations in G. W. are apparently a clinical counterpart, may result from comparable augmentation of the disposal of estrogen.

The absolute magnitude of the increase in thyroxine-binding by TBP may not have been as great in the patients herein described as in normal pregnancy since, as compared to values in the sera of normal nonpregnant controls, TBP activity was apparently significantly increased in the sera of postmenopausal and hypopituitary subjects prior to the administration of estrogen. Substantiation of the finding of increased thyroxine-binding by TBP during the postmenopausal and hypopituitary states is being sought in a larger group of patients, since it suggests, as one might expect, that factors other than estrogens are concerned with the regulation of TBP activity.

Increases in thyroxine-binding by TBP notwithstanding, administration of diethylstilbestrol did not reproduce completely the alterations in thyroidal economy which occur during normal pregnancy. Like women in the first half of pregnancy, euthyroid subjects receiving estrogen displayed an increase in the serum concentration of PBI with no accompanying increase in BMR. However, unlike pregnant women, they displayed no augmentation in the thyroidal uptake of I^{131}. In rats, administration of the synthetic estrogen, diethylstilbestrol, does not induce an increase in the thyroidal accumulation of radioiodine, although augmentations of uptake follow the administration of the naturally occurring estrogens, estrone and estriol (22, 23). In man, estrogens of the nature and quantity secreted during pregnancy may stimulate thyroidal uptake of I^{131}. Alternatively, it is possible that other hormonal changes which occur during pregnancy, or the presence of the conceptus itself, may account for the increased thyroidal accumulation of radioiodine. In this regard, the data of Greer appear to exclude the possibility that the placenta itself secretes TSH (24).

The increased concentration of serum PBI in pregnancy has been shown to consist of butanol-extractable and presumably, therefore, thyroxine-like material. Comparable fractionation of serum has not been made in the present patients, or in those whose PBI levels had previously been reported to have increased during administration of diethylstilbestrol (9, 10).

Assuming, as seems likely, that the iodinated material is indeed largely composed of thyroxine, the mechanism remains to be determined whereby diethylstilbestrol is capable of inducing an increase in the concentration of thyroid hormone in plasma without concurrently increasing the thyroidal uptake of I^{131}. Several possible explanations may be categorized as follows: a) a decrease in the peripheral degradation of thyroid hormone, b) an increase in the production and release of thyroid hormone, and c) an increased release of hormone, independent of a change in production. It would be anticipated that, were the peripheral degradation of hormone diminished by diethylstilbestrol, increases in the PBI level would be

noted in patients with myxedema receiving constant doses of exogenous hormone. In the present study, only 1 in 3 patients in this category demonstrated a distinct increase in PBI concentration during therapy. Similar failure of this agent to augment the level of PBI in the myxedematous subjects studied by Engstrom and Markardt (10) suggests that administration of this estrogen (with the consequent increase in thyroxine-binding by TBP) is not regularly associated with diminution in the peripheral rate of turnover of thyroxine. Observations in a greater number of comparable patients, as well as measurements of the influence of diethylstilbestrol on the distribution and rate of turnover of I^{131}-labelled thyroxine, are now in progress.

Augmented thyroidal production of hormone might occur if diethylstilbestrol diminished renal excretion without altering thyroidal accumulation of iodine. Data concerning the effects of this agent or of naturally occurring estrogens on the renal metabolism of iodine are scant. However, in rats, estrogens have little if any effect on this function (25).

Diethylstilbestrol might also induce a dissociation of the thyroidal response to tropic stimulation, resulting in the augmentation of hormonal release, but not of hormonal production in response to TSH. Alternatively, this agent might directly stimulate the release, but not the manufacture of hormone. In regard to the latter hypothesis, it has been demonstrated in rats that a portion of glandular thyroxine is "free," *i.e.*, not incorporated in the thyroglobulin molecule (26, 27). The concentration of this butanol-extractable thyroxine in the thyroid gland considerably exceeds that in the plasma. Recent observations suggest that the thyroglobulin molecule binds thyroxine in a butanol-dissociable complex which, *in vitro*, competes for the hormone with the proteins of plasma (28). Thyroid plasma-concentration ratios for "free" thyroxine might then depend on the relative thyroxine-binding capacities of the thyroglobulin within the gland and of the proteins in the plasma perfusing it. Augmentation of thyroxine-binding by TBP could then facilitate the passage of thyroxine from the gland into the plasma, and thereby accelerate the rate of hormonal release.

Association of an increased serum PBI level and an unchanged BMR is perhaps the most puzzling complex of findings noted during administration of diethylstilbestrol, and one which the present patients share with women during the first half of pregnancy. In addition, several patients in the present study demonstrated distinct reductions in BMR during and shortly following cessation of estrogenic therapy. Despite the failure of the BMR in these instances to return to control values during the recovery period, these changes are difficult to ascribe to training, not only because of their magnitude but also because the patients concerned had already had considerable recent experience with the metabolism test. Furthermore, in

at least 2 patients reversible signs and symptoms of hypometabolism developed coincident with the reduction in BMR. It is perhaps worthy of note that both were patients whose thyroidal reserve may be considered negligible. The first (M. McC.) had treated myxedema, and the second (V.C.) demonstrated no augmentation of the serum PBI level or of thyroidal I^{131} uptake following administration of TSH (29). It is apparent that the ability of diethylstilbestrol and of pregnancy to effectuate a dissociation of the usual quantitative relationship between serum PBI concentration and basal oxygen consumption requires additional study.

The present findings suggest that the marked augmentation of thyroxine-binding by TBP which occurs during pregnancy, may at least in part result from the influence of endogenous estrogen. Nevertheless, the functional consequences of this alteration are far from apparent. It seems likely, however, that continued investigation of thyroid-ovarian interrelationships, particularly with regard to the effects of ovarian hormones on the kinetics of iodine metabolism in man, may shed light on the function of TBP, as well as on those puzzling alterations of thyroidal economy which occur during pregnancy.

SUMMARY

1. The occurrence during normal pregnancy of an augmentation of thyroxine-binding by the specific thyroxine-binding protein of plasma, TBP, has been confirmed.

2. Diethylstilbestrol, when administered to patients with a variety of endocrinopathies in a dosage of 30 mg. daily for periods of four to eight weeks, induced alterations in thyroxine-binding by TBP comparable to those which occur during pregnancy.

3. This effect of diethylstilbestrol is not dependent on normal functioning of the thyropituitary axis, since it was noted in patients with hypopituitarism and with treated primary myxedema.

4. Other effects of diethylstilbestrol on thyroidal economy have been described, and their possible relation to altered thyroxine-binding by TBP has been discussed.

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TESTS FOR HYPERPARATHYROIDISM: TUBULAR REABSORPTION OF PHOSPHATE, PHOSPHATE DEPRIVATION, AND CALCIUM INFUSION*†

E. L. CHAMBERS, JR., M.D., GILBERT S. GORDAN, M.D., PHD., LEON GOLDMAN, M.D. AND E. C. REIFENSTEIN, JR., M.D.,
with the technical assistance of JEANETTE OMI, B.S., AND E. MARTINEZ, B.S.
The Departments of Medicine and Surgery, University of California School of Medicine, San Francisco, and The Squibb Institute for Medical Research, New Brunswick, N. J.

CONCEPTS of the mechanisms and the manifestations of hyperparathyroidism are still in the process of evolution. This situation is not surprising, for only thirty years have elapsed since the first successful removal of a parathyroid adenoma by Mandl from a patient with osteitis fibrosa cystica. The subsequent demonstration by Albright, Bauer, Ropes and Aub (1) that the parathyroid hormone causes increased urinary excretion of calcium and phosphate led to the recognition of nephrolithiasis as a more common clinical complication of hyperparathyroidism. Furthermore, it has since been shown that chemical hyperparathyroidism can exist without apparent osseous or renal involvement (2).

Experience has demonstrated that prolonged or severe hyperparathyroidism frequently produces progressive and irreversible renal damage. This realization has inspired a search for criteria and procedures by which hyperparathyroidism can be diagnosed with greater certainty, in order to detect the earliest and mildest forms in which a complete cure still can be achieved, and to resolve the large group of atypical and latent cases in which the diagnosis is obscure and difficult.

For these objectives, three new tests have been proposed: 1) the tubular reabsorption of phosphate, 2) phosphate deprivation, and 3) calcium tolerance. The purpose of this report is to present our evaluation of these diagnostic procedures in patients without renal insufficiency, with and without parathyroid disease.

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METHODS AND PROCEDURES

A. *Diagnostic Tests*

1. *Tubular reabsorption of phosphate (TRP)*

Albright *et al.* in 1929 (1) demonstrated the phosphate diuretic effect of parathyroid extract (3a). Harrison and Harrison in 1941 (3b) were able to show that parathyroid extract causes a decreased reabsorption of phosphate in the kidney tubules. In 1950 Crawford *et al.* (4) suggested that parathyroid function might be estimated through measurement of the percentage of phosphate filtered by the glomeruli which is reabsorbed by the renal tubules. This test was applied to the study of parathyroid tumors by Sirota in 1953 (5) and by Schaaf and Kyle in 1954 (6). In both studies, patients with parathyroid adenomas demonstrated distinctly low TRP, which was corrected by removal of the adenomas. Nordin and Fraser (7) employed the phosphate-to-creatinine clearance ratio for the same purpose. Mathematically, the

$$\text{TRP} = 1 - \frac{\text{phosphate clearance}}{\text{creatinine clearance}}$$

as may be seen from the following calculation:

$$\frac{\text{Cl P}}{\text{Cl C}} = \frac{\dfrac{\text{UP} \times \text{UV}}{\text{SP} \times t}}{\dfrac{\text{UC} \times \text{UV}}{\text{SC} \times t}} = \frac{\text{UP} \times \text{SC}}{\text{UC} \times \text{SP}}$$

$$\text{TRP} = \frac{\text{filtered P} - \text{excreted P}}{\text{filtered P}} = \frac{(\text{GF}/t \times \text{SP}) - (\text{UP} \times \text{UV}/t}{(\text{GF}/t \times \text{SP})} = 1 - \frac{\text{UP} \times \text{UV}/t}{\dfrac{\text{UC} \times \text{UV}}{\text{SC} \times t} \times \text{SP}} = 1 - \frac{\text{UP} \times \text{SC}}{\text{UC} \times \text{SP}}$$

$$\text{TRP} = 1 - \frac{\text{Cl P}}{\text{Cl C}}$$

and

$$\% \text{ TRP} = 100\left(1 - \frac{\text{UP} \times \text{SC}}{\text{UC} \times \text{SP}}\right)$$

where Cl is the clearance in ml./min.; P is the inorganic phosphate concentration (mg./ml.); C is the creatinine concentration (mg./ml.); U = urine; S = serum; V is the volume in ml.; t is the time in minutes; and GF is the glomerular filtrate (ml.) (endogenous creatinine clearance).

Use of this shortened formula for estimation of TRP has distinct advantages. As pointed out by Nordin and Fraser, elimination of urine volume and time from the final calculation avoids errors caused by inexact collection, timing, or incomplete emptying of the bladder. Since the glomerular filtration rate is estimated from the endogenous creatinine clearance, TRP measured by this formula is only meaningful over normal ranges of creatinine clearance. Our own observations have been confined, therefore, to patients without renal insufficiency (serum creatinine level, 1.3 mg. per 100 ml. or less).

2. *Phosphate deprivation*

In 1932 Albright, Bauer, Claflin and Cockrill (8) demonstrated that in patients with hyperparathyroidism which subsequently was proved at operation, a very high phos-

phate intake abolished hypophosphatemia, hypercalcemia and hypercalciuria. After fifteen days of high phosphate administration the patients had lost all of the manifestations of chemical hyperparathyroidism, except the hyperphosphaturia (which was increased still further by the excessive phosphate intake). At the end of the study, it would have been impossible to make the diagnosis of hyperparathyroidism from the traditional criteria of hypercalcemia with hypophosphatemia.

Since the average American diet is often rich in phosphate it occurred to one of us (E. C. R.) that this high phosphate intake might similarly mask the diagnosis of hyperparathyroidism through the borderline nature of the resulting serum mineral levels. By reversing the procedure of Albright *et al.* (*i.e.*, by reducing the phosphate intake) it might be possible to unmask the serum calcium and phosphate abnormalities in "hidden" hyperparathyroidism, thus facilitating the diagnosis. It was assumed, furthermore, that in patients with normally functioning parathyroid glands there would be compensatory adjustments to the dietary restriction of phosphate so that approximately normal serum levels would be maintained, in contrast to those that would appear when there was primary hyperfunction of the parathyroid glands.

Therefore, in 1955 the phosphate deprivation test was devised by one of us (Reifenstein (9)) to test this hypothesis. In the test, the reduction in the serum phosphate level is brought about by a standardized restriction of phosphate intake; this restriction also facilitates the absorption of calcium from the gastro-intestinal tract (10). The serum calcium and phosphate levels, the amount of phosphate excreted in the urine, and the TRP are taken as indices for the test.

The test is performed as follows. The subject under study eats an identical diet for three to six days. The diet must be low in phosphorus, normal in calcium, and adequate in calories. The 24-hour urine collections made on days 0, 3 and 6 are analyzed for phosphate and creatinine content. Blood samples are analyzed for calcium, total protein, inorganic phosphorus and creatinine on days 0, 3 and 6. A diet suitable for this test originally was devised by Miss Shirley L. Wells; subsequent minor modifications have been made to improve the management of the regimen. The diet is as follows:

Low phosphate diet

1,920 Calories (plus added sugar and butter); 58 Gm. protein; 430 mg. phosphate; 700 mg. calcium

Breakfast: 2 bananas, 3 egg whites, 1 slice Vienna bread, 1 pat butter, 8 oz. pineapple juice, 5 prunes, coffee or tea, sugar, salt, pepper.

Lunch: 2 egg whites, ⅔ cup cooked rice, 1 slice Vienna bread, 2 pats butter, 5 oz. tomato juice, ½ oz. gelatin, 3 oz. applesauce, ½ oz. cranberry jelly, ½ pkg. Jello, 1 oz. lemonade, coffee or tea, sugar, salt, pepper.

Dinner: 3 egg whites, ⅔ cup cooked rice, 1 slice Vienna bread, 2 pats butter, ½ cup blueberries, ½ oz. cranberry jelly, 1 banana, ½ pkg. Jello, 6 oz. apple juice, 1 oz. lemonade, coffee or tea, sugar, salt, pepper, 6 Gm. calcium gluconate.

In persons with normal parathyroid glands, it was anticipated that there would be no change in the serum calcium concentration, a moderate fall in the serum phosphate level, and a marked reduction in the urinary phosphate excretion following several days of such a very low phosphorus intake. In contrast, in persons with hyperfunctioning parathyroid glands under the same regimen, it was postulated that there would be a moderate rise in the serum calcium concentration, a moderate fall in the serum phosphate level, and only a moderate decrease in the excessive urinary phosphate excretion. In hyper-

parathyroidism, therefore, the phosphate deprivation would accentuate the deviations of the serum calcium and phosphate levels from the normal values, and thereby, would aid in establishing the diagnosis in cases in which these serum mineral concentrations had not been consistently and convincingly abnormal.

3. *Calcium tolerance*

In 1924 Salveson *et al.* (11) noted that serum phosphate levels rose after calcium chloride infusions in the dog. Baylor and associates in 1950 (12) observed a decreased excretion of phosphate in the urine following calcium gluconate infusions in man. Schilling and Laszlo in 1951 (13) employed a standardized small calcium gluconate infusion in the study of skeletal avidity for calcium, and in 1952 Howard *et al.* (14) introduced the intravenous calcium tolerance test for the systematic study of parathyroid disorders. Several workers have further extended these observations—Justin-Besançon *et al.* (15); Nordin and Fraser (7); Goldman and Bassett (16); Kyle *et al.* (17); and our own experience thus far in 60 studies.

We administered the calcium intravenously to the fasting patient as 20 per cent calcium gluconogalactogluconate[1] in 500 ml. of 0.9 per cent sodium chloride solution over a four-hour period. Samples of blood serum were collected at 0, 4, 8 and 24 hours; and a 24-hour specimen of urine was collected on the day preceding and on the day following the infusion, and on the infusion day during the periods 0–4, 4–8, 8–12, and 12–24 hours. Blood and urine samples were analyzed for calcium, phosphate and creatinine. In most instances the infusion contained 12.4 mg. of calcium per Kg. of body weight (0.66 ml. of 20 per cent Neocalglucon per Kg.), since this dose elicited the same responses as a larger dose (18.6 mg. per Kg.) and induced an adequate but not potentially dangerous rise of the serum calcium level. Infusions were not given to patients with cardiac or renal disease, or with serum calcium levels higher than 14.2 mg. per 100 ml.

B. *Chemical Determinations*

Calcium was determined by the method of Kramer and Tisdall (18), as modified by G. W. Clark (19). Serum and urine phosphates were analyzed by the procedure of Fiske and SubbaRow (20), and tissue phosphate by the method of Stone (21). Creatinine was determined by the Jaffe alkaline picrate technic, as modified by Hopper (22), using a Folin-Wu filtrate. Picrate, which has been made sufficiently alkaline by the addition of 10 per cent NaOH to turn yellow, is added to an aliquot of filtrate containing 0.01 to 0.1 mg. of creatinine. The intensity of the red color produced after twenty minutes at room temperature is read in a Klett-Summerson colorimeter with a green filter.

C. *Clinical Material*

1. *Control subjects*

Persons who appeared to be in good health and patients with disorders not considered to involve the parathyroid glands were studied to provide a baseline for the findings in the patients with parathyroid disease.

2. *Patients with hyperparathyroidism*

The chemical measurement and diagnostic procedures under consideration were evaluated in 10 patients who were proved subsequently at surgery to have hyperparathyroid-

[1] Neocalglucon-Sandoz, generously supplied by Mr. Harry Althouse, Sandoz Pharmaceuticals, San Francisco, California.

ism. Eight of the patients had single adenomas, and 2 had diffuse hyperplasia of all of the parathyroid glands. One of the patients had the osseous complications of hyperparathyroidism, as indicated by elevated serum alkaline phosphatase levels and by roentgenographic evidence of demineralization and cysts of the bones. The renal complications of hyperparathyroidism were present in all 10 patients, with renal calculi in 9 and nephrocalcinosis in 2, but renal function was normal in all, as measured by serum levels of creatinine and nonprotein nitrogen, creatinine clearance, and phenolsulfonphthalein excretion. One patient had 3 parathyroid glands removed surgically prior to the excision of a parathyroid adenoma, and then manifested postoperative hypoparathyroidism with tetany until adequate treatment with calciferol (vitamin D_2) was instituted.

3. *Patients with hypoparathyroidism*

The diagnostic procedures were evaluated in 22 patients with hypoparathyroidism (21 cases with postoperative parathyreoprivia and 1 patient with idiopathic parathyroid hypofunction). Twenty-one were receiving treatment with calcium salts, calciferol or dihydrotachysterol, usually with added aluminum salts to bind dietary phosphate.

RESULTS AND DISCUSSION

1. *Traditional criteria for hyperparathyroidism*

It should be pointed out at the outset that a reliable demonstration of hypercalcemia, assuming a normal serum protein level, remains of cardinal importance in the diagnosis of hyperparathyroidism. Figure 1 illustrates this point. In this graph 303 control total serum calcium determinations (made on 109 normal subjects, 42 patients with osteoporosis and 65 patients with urolithiasis) are shown, and 82 determinations in 10 patients with surgically proved hyperparathyroidism. As may be seen, there is an

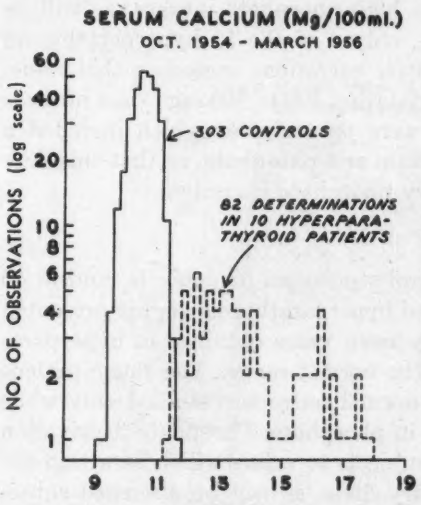

FIGURE 1

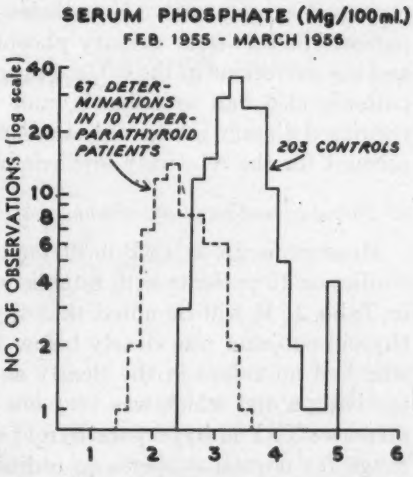

FIGURE 2

excellent over-all separation between the two groups, although a small but definite overlap is observed. Within this equivocal zone fall all the determinations on one hyperparathyroid subject, and half the determinations on a second patient, also with mild hyperparathyroidism; in both, the diagnosis was confirmed at operation.

A low serum phosphate level has been considered a characteristic feature of hyperparathyroidism, except in the presence of renal insufficiency. In this series, in which hypercalcemia was often mild, hypophosphatemia proved inconstant. This is illustrated in Figure 2, which shows a considerable overlap in the distribution curves of 203 control serum phosphate values, and 67 measurements in 10 patients with established hyperparathyroidism. *Only 4 of these 10 patients with proved hyperparathyroidism had serum phosphate levels consistently below the equivocal zone.* In 2, from whom parathyroid adenomas were subsequently removed, no phosphate value below 2.8 mg. per 100 ml. was ever obtained either in our laboratory or in duplicate determinations in two other laboratories.

Hypercalciuria (more than 150 mg. per twenty-four hours) was present in 9 of the 10 cases of established hyperparathyroidism; in the tenth patient, in whom severe calcium restriction had been enjoined because of nephrolithiasis, the urinary calcium excretion ranged from 141 to 179 mg. in four separate 24-hour determinations.

Hyperphosphaturia is difficult to evaluate as a criterion for hyperparathyroidism. Urinary phosphate excretion in normal subjects was found to be as high as 1,120 mg. per twenty-four hours. The subjects in whom this was noted all appeared to have high phosphate intakes, as will be discussed subsequently. Nonetheless, only 4 of the 10 hyperparathyroid patients had 24-hour urinary phosphate excretions exceeding this value, and the excretions in the other 6 ranged from 400 to 800 mg. Most of these patients also had urolithiasis, and were on regimens which included a restricted dietary intake of both calcium and phosphate, so that this may account for the relatively low urinary phosphate excretion.

2. *Tubular reabsorption of phosphate*

Measurements of TRP in 66 control studies on 53 subjects, and in 40 studies on 10 patients with established hyperparathyroidism are presented in Table 1. It will be noted that the mean value obtained in hyperparathyroid subjects was clearly below the normal range. The single patient who had no values in the clearly abnormal range was studied only while receiving a diet which was very low in phosphate. Phosphate deprivation increases TRP in hyperparathyroid subjects to values which lie within the range for normal subjects on ordinary diets, as will be discussed subsequently (*cf.* phosphate deprivation). Furthermore, even those patients who had TRP values not very far below normal during active hyperpara-

TABLE 1. TUBULAR REABSORPTION OF PHOSPHATE

No. of studies	No. of cases	Category	% TRP, mean ± S.E.
18	13	Normal	84.7 ± 0.9 (78–90)
21	17	Osteoporosis	83.7 ± 0.6 (79–89)
27	23	Urolithiasis	84.4 ± 0.7 (78–91)
40	10	Hyperparathyroidism	65.0 ± 1.3 (41–82)
24	12	Hypoparathyroidism (serum PO_4, 4.3 or above)	91.5 ± 1.0 (79–99)
28	10	Hypoparathyroidism (serum PO_4, 4.2 or less)	84.8 ± 1.1 (74–94)

$$\% \text{ TRP} = \left[1 - \frac{\text{urine } PO_4 \times \text{serum creatinine}}{\text{urine creatinine} \times \text{serum } PO_4}\right] \times 100$$

thyroidism, demonstrated persistently higher, and clearly normal, values beginning one or two weeks after removal of the abnormal parathyroid tissue, and continuing throughout the period of observation thereafter (Fig. 3).

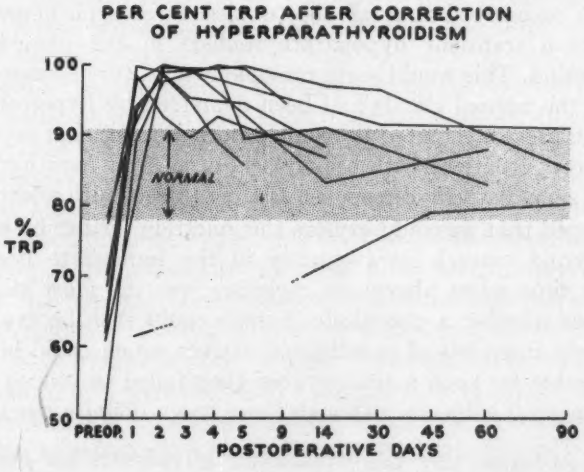

FIGURE 3

Despite the good separation demonstrated between TRP values for normal and for hyperparathyroid subjects, we observed a repeatedly low TRP in a patient with sarcoidosis, and in a small group (5 patients) who had an unexplained low level of serum phosphate but normal levels of serum calcium and alkaline phosphatase. In 1 of the latter, TRP was raised from 68 to 97 per cent and 24-hour urinary phosphate excretion was reduced from 910 to 68 mg. per twenty-four hours by six days of the phosphate deprivation diet, as described in the next section. During this time the patient's serum phosphate level did not change.

Eight of the 10 patients with hyperparathyroidism were found to have parathyroid adenomas at operation, and 2 had diffuse hyperplasia of all the parathyroid glands. One of the latter group continued to have hypercalcemia, hypercalciuria and hypophosphatemia after operation and showed no change in TRP. The other 9 patients, however, showed a striking increase in TRP, almost to unity, in the immediate postoperative period (Fig. 3). In 1 patient, three parathyroid glands had been surgically removed prior to excision of a parathyroid adenoma. The TRP remained elevated almost to 100 per cent until adequate treatment with calciferol was instituted. In the other 8 patients, TRP subsequently returned to normal levels, as shown in Figure 3, and has remained normal to the present time.

The distinct rise in TRP immediately after corrective surgery is of considerable interest, since it involves virtual cessation of urinary phosphate excretion at a time when the serum phosphate level is rising but glomerular filtration is essentially unchanged. Thus, a presumably increased amount of phosphate is being filtered by the glomeruli and almost all that is filtered is reabsorbed through the tubules. Such a phenomenon probably reflects a transient hypoparathyroidism in the immediate postoperative period. This would seem reasonable if it were assumed that the function of the normal glands had been depressed by hypercalcemia and that a few days were required to regain a normal functional capacity. It is interesting that 1 patient with hyperplasia of all four parathyroid glands showed the same pattern of response as the subjects with adenomas.

It was hoped that we could explore this question further by administering parathyroid extract intravenously in the immediate postoperative period at a time when phosphate excretion was the most strikingly reduced, to see whether a phosphate diuresis could then be evoked. However, the only three lots of parathyroid extract which could be obtained[2] were unsuitable for such a test because they failed to induce phosphate diuresis in normal subjects, although there was a definite rise in the level

[2] Parathyroid Extract Lilly, Lots #7165-663522, #2119-653775, and #6039-638674.

of serum calcium. This observation is of particular importance, in that it shows clearly that the hypercalcemia induced by parathyroid extract need not be mediated by phosphate diuresis. This finding is in accord with experimental studies by Munson (23), who suggested that separate factors may account for these two parathyroid functions.

As Table 1 indicates, 52 measurements of TRP were made in 22 patients with hypoparathyroidism (postoperative and idiopathic). It will be noted that the hypoparathyroid subjects with high serum phosphate levels had a statistically higher TRP than either the control group, or the hypoparathyroid subjects with normal serum phosphate levels. In the only observation which could be made on a completely untreated hypoparathyroid patient, a TRP of 99 per cent was obtained—a value comparable to that observed immediately after surgical correction of hyperparathyroidism. Hypoparathyroid patients with normal serum phosphate levels had essentially normal values for TRP, and were not statistically different from the control group.

There was no apparent difference in TRP between patients receiving calciferol and those receiving dihydrotachysterol. TRP is not proposed as a criterion for adequacy of treatment of hyperparathyroidism, since the aim—reduction of the serum phosphate level—may be attained by reducing the absorption of phosphate in the intestine as well as by increasing the urinary excretion of phosphate.

3. *Phosphate deprivation*

The standardized low phosphate diet was administered to 5 normal subjects for a six-day period. Six similar studies were carried out in 5 patients with proved hyperparathyroidism. Changes in serum calcium and serum phosphate levels, urinary phosphate excretion, and TRP during these studies are shown in Table 2.

It will be seen that restriction of phosphate intake resulted in a definite fall in the serum phosphate level in all 5 normal subjects. In contrast, the serum phosphate level rose or fell only slightly in the 4 patients with hyperparathyroidism who initially had low values. The serum phosphate level did not fall below the normal range in any of the 5 normal subjects, whereas it fell to a definitely abnormal level in 1 hyperparathyroid patient in whom the phosphate level initially was in the normal range. (It should be recalled that the normophosphatemia in these patients with proved hyperparathyroidism was not associated with impaired renal function.) During the second three days of the study there was no further significant change in serum phosphate level. In 1 subject in whom daily serum phosphate determinations were made, almost all the fall in serum phosphate concentration occurred after a single day on the diet. The most important

observation was the precipitation of definite hypophosphatemia in a patient who previously had a normal serum phosphate level (which at that time obscured the diagnosis of hyperparathyroidism, subsequently confirmed at operation).

The serum calcium levels of the normal subjects during the period of deprivation remained within the normal range. In contrast, the already elevated serum calcium values rose slightly to markedly in 5 of the 6 hyperparathyroid patients and showed a slight drop in the sixth. Phosphate deprivation thus served to accentuate hypercalcemia.

TABLE 2. PHOSPHATE DEPRIVATION TEST

Case	Serum phosphate (mg./100 ml.)			Serum calcium (mg./100 ml.)			Urine phosphate (mg./24 hrs.)			TRP		
	Baseline	3 days	6 days	Baseline	3 days	6 days	Baseline	3 days	6 days	Baseline	3 days	6 days
Normal Subjects												
LM	3.4	2.7	2.7	10.7	10.5	10.5	540	288	270	89.3	93.7	93.4
GG	3.9	3.4	3.2	10.1	10.5	10.3	1118	394	326	78.2	92.0	84.3
CE	3.7	3.0	3.0	10.7	10.5	10.6	800	236	252	84.4	92.6	91.4
OJ	3.9	3.6	3.7	10.2	10.1	10.2	709	200	282	88.4	92.4	88.3
ME	4.1	3.8	3.7	10.3	10.3	10.2	780	550	382	84.3	89.4	91.4
Hyperparathyroid Subjects												
SA	2.4	2.3	2.2	12.8	12.9	13.2	1085	660	525	68.3	80.5	83.5
HC_1	3.1	—	2.2	11.6	—	11.9	804	—	292	66.2	—	84.4
KW	2.0	2.2	2.1	12.5	12.4	13.0	1140	900	530	61.0	70.8	78.1
AG	2.7	2.8	2.8	13.2	13.3	12.4	750	378	364	62.1	83.6	83.9
HC_2	3.5	3.0	—	12.2	12.7	—	655	355	—	70.0	78.3	—
RC	2.2	2.2	—	13.6	15.3	—	1430	385	—	51.0	65.0	—

The urinary phosphate excretion fell in both the normal subjects and the hyperparathyroid patients. One of the normal subjects showed a marked additional reduction in phosphate excretion during the second three days of the restricted phosphate intake. The patients with hyperparathyroidism tended to have a higher urinary phosphate excretion than the normal subjects after three days on the low phosphate diet. There was no clear-cut separation between the response of urinary phosphate excretion of normal subjects and that of hyperparathyroid patients after either three or six days of phosphate deprivation.

The changes in TRP were interesting. In the normal subjects the baseline TRP ranged from 78 to 89 per cent, but after three days of phosphate deprivation the TRP ranged from 89 to 95 per cent. In the hyperparathyroid subjects, the baseline TRP ranged from 51 to 70 per cent; after three days of phosphate restriction the highest TRP was 83 per cent. Thus, the TRP

following phosphate deprivation also effected a clear-cut separation between the normal and hyperparathyroid subjects. The TRP values for the two groups after six days of phosphate restriction showed a good separation, but by this time TRP had begun to fall in the control group and was still rising in the hyperparathyroid group, so that the contrast was not as striking as on the third day, although still definite.

It is of interest that the lower the initial tubular reabsorption of phosphate in either the normal subjects or the hyperparathyroid patients, the greater seemed to be the increase in TRP induced by phosphate deprivation. This suggests that the efficiency of phosphate conservation is enhanced in the presence of restricted phosphate intake through increasing TRP because of decreased parathyroid activity.

4. *Calcium tolerance*

Sixty intravenous calcium tolerance tests were performed. In Table 3 and Figure 4 are shown the phosphate responses in 20 control studies, in

TABLE 3. CALCIUM TOLERANCE TEST (HOWARD): PHOSPHATE RESPONSES

	20 controls	12 Hypoparathyroid patients	10 Hyperparathyroid patients
Rise in serum phosphate level (mg./100 ml.)	0.9–2.8	0.3–2.3 (10 of 12 = 0.9 or more)	0.4–1.2 (7 of 10 = <0.9)
Attained serum phosphate level (mg./100 ml.)	3.6–6.0	4.2–6.5	2.6–4.1 (7 of 10 = <3.6)
Change in urinary phosphate excretion from baseline (mg./24 hrs.)	decreased (one exception) (−79%–+4%)	7 of 12 decreased (−33%–+119%)	8 of 10 decreased (−55%–+34%)

12 studies on 10 hypoparathyroid patients (9 postoperative and 1 idiopathic), and in 10 subjects with hyperparathyroidism.

In 7 of 10 patients with surgically proved hyperparathyroidism, the serum phosphate rise after calcium infusion was less than the smallest rise in the control series. On the other hand, 3 patients with proved hyperparathyroidism had normal serum phosphate rises, checked by phosphate determinations in our own and two other laboratories. The group with subnormal phosphate rises included 1 patient with parathyroid hyper-

plasia, and 6 with adenoma. The group with normal rises included a second patient with parathyroid hyperplasia, and 2 with adenoma.

Urinary phosphate responses were inconsistent in the hyperparathyroid patients (Table 3), but in 8 of 10 subjects there was about the same degree of phosphate antidiuresis as in the controls. The response in the hypoparathyroid group was not consistent, but in 5 of 12 studies there was an increased urinary phosphate excretion for the 24-hour period following the calcium infusions. In Figure 4 the serum and urinary phosphate responses

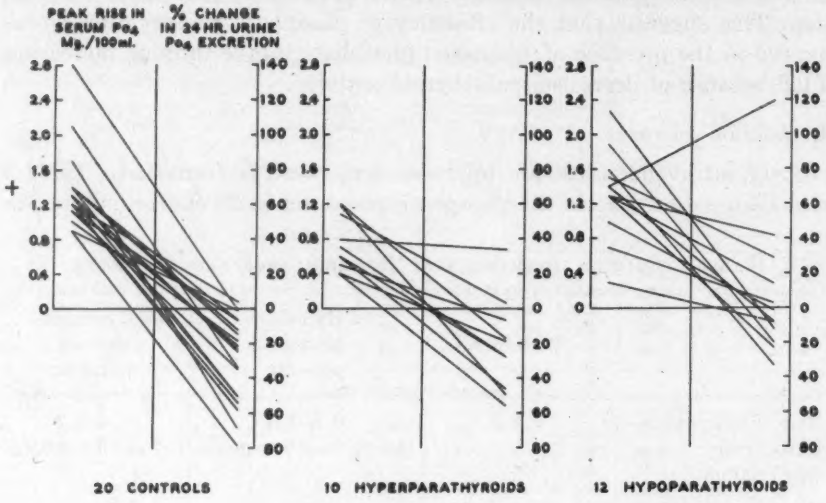

FIGURE 4

to the infusions in our control, hyperparathyroid and hypoparathyroid groups are plotted in the manner employed by Howard (14). Although each of the three groups, plotted in this way, appears to be different from the other two, there is no striking uniformity within the groups.

The rise of serum phosphate concentration and the decline in urinary phosphate excretion following calcium infusion resembles the chemical changes in hypoparathyroidism. It has been suggested (14), therefore, that the rise in serum phosphate concentration which follows calcium infusions in normal subjects is a result, at least in part, of transient depression of parathyroid function by the hypercalcemia which has been induced. The present study would indicate that this could not be one of the important mechanisms, since in the absence of functioning parathyroid tissue similar rises in the level of serum phosphate occurred in 10 of the 12 studies on patients with hypoparathyroidism.

On the other hand, the phosphate rise almost certainly cannot be at-

tributed to reduced glomerular filtration following the calcium infusions. In our series, there was no difference in urine flow or in glomerular filtration rates, as measured by endogenous creatinine clearances, before and after the calcium infusions.

Two patients who had subnormal rises in the serum phosphate level after calcium infusion, prior to removal of parathyroid adenomas, were studied postoperatively by the same technic. One patient, as shown in Table 4, still displayed an abnormal serum phosphate response sixteen days postoperatively, but by forty-five days the response was normal. A second patient, studied on the sixth postoperative day, still had a subnormal rise

TABLE 4. CALCIUM TOLERANCE TEST FOLLOWING EXCISION OF PARATHYROID ADENOMA

WM, male, weight 89 Kg., dose 5 mg./Kg.

	Preop.	Postop. (16 days)	Postop. (45 days)
Serum calcium rise (mg./100 ml.)	1.2	1.7	1.9
Serum phosphate rise, (mg./100 ml.)	0.6	0.7	1.4
Urine phosphate fall (mg.)	446	373	317
Per cent of calcium load excreted	37	0	55

in the serum phosphate level. These findings are in accord with the more extensive observations of Howard (14).

On the other hand, 4 patients with osteomalacia, and 1 with idiopathic osteoporosis studied during pregnancy, displayed increases in serum phosphate concentration of 0.7 mg./100 ml. or less. Although these responses are similar to those found in hyperparathyroidism, the normal or low serum calcium levels should clearly differentiate osteomalacia.

The possibility was then considered that the patients who displayed subnormal rises in the level of serum phosphate after calcium infusion might also have depleted stores of intracellular phosphate, and therefore have less phosphate available for exchanges with the extracellular fluid. In an attempt to explore this possibility further, studies of total muscle phosphate in control and hyperparathyroid subjects are now being conducted and will be reported subsequently. This proposal is consistent with the clinical observation that certain patients with hyperparathyroidism have marked muscular weakness.

SUMMARY AND CONCLUSIONS

1. Demonstration of subnormal tubular reabsorption of phosphate (TRP) is of value in the diagnosis of hyperparathyroidism without renal impairment. TRP may be elevated to low-normal levels by severe phos-

phate deprivation in hyperparathyroidism. It may be low in osteomalacia, sarcoidosis, and in some disorders of unknown origin.

2. The responses to a standardized low-phosphate diet may be of diagnostic value in hyperparathyroidism. With this diet the serum calcium level is increased to a greater extent, and TRP to a lesser extent, than in normal individuals.

3. The intravenous calcium tolerance test performed in 10 hyperparathyroid patients demonstrated a subnormal rise of the serum phosphate level in 7 instances. The rise in serum phosphate concentration cannot be attributed to a transient depression of parathyroid function, since it is also observed in hypoparathyroid subjects.

4. Normal serum phosphate levels were demonstrated in patients with proved hyperparathyroidism without renal insufficiency.

5. Although hypercalcemia remains the most reliable of the traditional diagnostic criteria, it is not pathognomonic of hyperparathyroidism. Moreover, some patients present such minimal degrees of hypercalcemia that the use of further tests is helpful.

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GENETIC AND ENVIRONMENTAL FACTORS IN CRETINISM: A CLASSIFICATION*

JOHN B. STANBURY, M.D. AND ANDRIES QUERIDO, M.D.

The Medical Services of the Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts; and the Department of Endocrinology and Metabolism, Academisch Ziekenhuis, Leiden, The Netherlands

THE term "cretinism" lacks precise definition. Even the origin of the term is obscure (1). According to Means (2), a cretin is one who "suffers from athyreosis from intra-uterine life or early in infancy at best." This definition has the advantage that the exact time of thyreoprivia in development is not implied, nor is a functioning thyroid gland at a later date excluded. Thus, a diagnosis of cretinism is not incompatible with the finding of a functioning thyroid, but certain characteristic developmental defects must be present before the diagnosis can be made.

We propose to define a cretin as a patient who has permanent retardation in development of the skeleton or central nervous system resulting from thyroid deficiency which existed during fetal or early neonatal life. Some observers, refusing to attribute the clinical findings of cretinism entirely to thyroid failure, postulate other constitutional abnormalities as well, but there appears to be little justification for this point of view.

The varying manifestations of cretinism suggest various causes for the disorder. Thus, cretinism was seen most commonly in close association with endemic goiter before the introduction of iodide prophylaxis, but it also occurs sporadically without goiter in all parts of the world, and Osler himself called attention to familial cretinism with goiter in nonendemic regions of the United States (3). Furthermore, the severity of the condition fluctuates widely among patients. Several recent studies have clarified to a degree the pathologic physiology of cretinism. This paper presents a classification based on such information as is presently available bearing upon the varied etiologies of the disease (Table 1).

PLACENTAL TRANSFER OF IODIDE AND THYROID HORMONES

The extent of the maternal contribution of thyroid hormone to the fetus is not known. The placenta normally concentrates iodide, but by no

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TABLE 1. CLASSIFICATION OF CRETINISM

I.	Anatomic Dysgenesis of the Thyroid
	A. Congenital athyreosis
	B. Hypotrophic aberrant thyroid remnants
II.	Nutritional Hypothyroidism
	A. Iodine deficiency
III.	Inborn Errors of Metabolism
	A. Failure of organification of iodine
	B. Failure of coupling of iodotyrosines
	C. Lack of deiodination of iodotyrosines
	D. Other

means to a degree comparable to that of the thyroid. Logothetopoulos and Scott (4) found a concentration gradient of iodide between fetal and maternal blood of the rabbit and guinea pig of approximately 3 to 1, but could find no gradient for the rat. These observations have been confirmed by Friis and Hall (5) for the rabbit. Hall and Myant (6) found that the ratio of fetal to maternal serum concentration after administered I^{131}-labeled thyroxine did not exceed 0.022 before the nineteenth day of gestation, but became somewhat higher toward the end of pregnancy. The ratio of placental to maternal blood iodide, however, indicates only the equilibrium state and does not indicate the *rate* at which iodide is being transferred. It is possible that in conditions of iodide depletion, the placenta is able to compete more successfully with the maternal thyroid, but this seems doubtful. Rather, it is possible that the hyperplastic maternal thyroid of the iodine-deficient subject might actually succeed in withholding iodine from the fetus. In this regard, Postel (7) observed that when iodide was denied to the thyroid by feeding perchlorate to the pregnant guinea pig, the fetal thyroid became many times larger than the maternal gland, which scarcely enlarged at all under the conditions of his experiment.

Placental transfer of thyroxine or of triiodothyronine is, at best, a slow process. Friis and Hall (5), using chromatographic methods of identification, were unable to find any I^{131}-labled thyroxine in the fetal blood of guinea pigs one hour after administration into the maternal circulation. Postel (7) was able to demonstrate the placental transfer of only a small percentage of I^{131}-labeled triiodothyronine into the guinea pig fetus one hour after administration, and approximately the same after twenty-four hours. Peterson and Young (8) observed hyperplasia of the fetal guinea pig thyroid when the diet contained propylthiouracil. The fetal goiter was not entirely suppressed by adding 25 micrograms daily of thyroxine to the

diet. These experiments indicated that, in the dose given, thyroxine crossed the placenta in amounts sufficiently large to counteract in part the influence of the propylthiouracil. Recently, Grumbach and Werner (9) studied the effect of giving I^{131}-labeled thyroxine to pregnant human females at various times preceding delivery. Fetal and maternal thyroid glands were blocked by prior administration of large doses of iodide. During the first few hours after administration, the precipitable labeled iodine of the fetal serum was only 2 to 8 per cent of that in the maternal serum, but with the passage of time, labeled iodine slowly began to cross the placenta, and at one hundred and sixty-nine hours had reached about 49 per cent of the concentration in the maternal serum.

The fetal thyroid is a functioning structure after the twelfth to fourteenth week of gestation (10, 11) and appears to be able to supply an adequate amount of hormone, for normal children may be born of athyreotic mothers. On the other hand, there is no uniformity of opinion regarding the adequacy of placental transfer of hormone when the fetus is athyreotic. Customarily, the diagnosis of cretinism in non-endemic regions is not made until the third or fourth week after delivery. Dorff (12) reported a cretinous child of 17 months, with a normal twin sibling, who had retardation of bony development which indicated arrest during fetal life; however, some if not all of the centers of ossification which were absent in his patient may normally be absent for the first postnatal month. It is possible that the mental defect in the sporadic cretin may be an associated one rather than a result of uterine thyreoprivia. At all events, early treatment may not suffice to prevent mental deficit, although excellent physical development may ensue.

CRETINISM FROM ANATOMIC DYSGENESIS OF THE THYROID

A. *Congenital athyreotic cretinism*

This is the usual type of cretinism in regions where goiter is not endemic. Most often there is no familial predilection, but there are reports of multiple cases in the same family (13). Moreover, Childs and Gardener (14) found an increased incidence of thyroid diseases of other types in relatives of patients with athyreotic cretinism. Pathologic study discloses no evidence of thyroid gland tissue, or only a fibrous remnant which may contain an occasional cluster of thyroid cells or a follicle buried deep within its substance.

The severity of the physical and mental retardation reflects the degree of thyreoprivia during uterine life, and how soon and how adequately replacement therapy was given in the postnatal period. Many of the poor

results which have been obtained from the use of thyroid in these patients stem from the fact that irreversible damage had already been done by athyreosis during critical and normally rapid phases of growth.

B. *Cretinism in association with congenital hypotrophic thyroid remnants*

Closely akin to congenital athyreotic cretins are those cases which have been well described and studied in detail by Weller (15), and McGirr and Hutchison (16). Similar patients were probably observed by Horst and von Harnack (17). The patients of McGirr and Hutchison (16) displayed the clinical features of mild cretinism or juvenile myxedema. They were found to have depressed serum concentrations of protein-bound iodine, and low metabolic rates. Study with I^{131} disclosed rapid accumulation and turnover of labeled iodine by small hyperfunctioning remnants of thyroid tissue. By means of radioiodine localization methods, these were found at the root of the tongue. They were considered to represent arrest in the embryonal development of the gland. These remnants were unable to undergo sufficient hyperplasia to meet fully the needs of the growing child.

McGirr and Hutchison (16) were unable to draw a sharp distinction between juvenile myxedema and cretinism in their patients. Rather, these conditions were considered oftentimes to result from the same developmental defect. The time of appearance of the signs and symptoms of hypothyroidism and their severity were thought to depend upon the amount of thyroid tissue which was present and its capacity to undergo hyperplasia. The embryonic development of the thyroid and the abnormalities of its organogenesis in relation to disease have recently been reviewed by Rogers (18).

CRETINISM FROM NUTRITIONAL DISORDERS

The cretinism of iodine deficiency

Endemic cretins, as classically described by de Quervain and Wegelin (19) (Fig. 1) were found in intimate association with endemic goiter in regions of the world where iodine deprivation is now thought to have been the causative factor. Typically, the endemic cretin occurred in families which had exhibited progressively severe endemic goiter in successive generations, as though the meager supply of iodine passed on from mother to child had finally run out. Animal experiments have indicated that the developmental findings of endemic cretinism can be reproduced readily by destroying both maternal and fetal thyroids with radioactive iodine (21).

Visible goiter is often present, and there is always histologic evidence of previous hyperplastic changes. Almost always there are adenomatous nodules, which vary in size and contain little or no colloid (22). There

is often considerable cystic degeneration and fibrosis. Indeed, de Quervain and Wegelin (19) considered many of their endemic cretins to be functionally athyreotic from atrophy of the gland in the first few years of life. The final clinical result may depend not only upon the intra-uterine damage, but also upon the functional capacity of the thyroid in postnatal life and the quantity of iodine which becomes available to the patient.

FIG. 1. Typical appearance of a goitrous endemic cretin from Sardinia. (From a study of cretinism commissioned by the King of Sardinia, 1848 (20).)

Many observers have found a theory of iodine deficiency inadequate to account for all the manifestations of endemic cretinism. While accepting an important role for iodine deprivation in these patients, they have indicated underlying predisposing factors. These factors, if indeed they exist, have not been further defined with certainty. A finding of possible significance was that of Costa *et al.* (23). Three out of 10 cretins studied in northern Italy were found to have a large amount of an iodinated substance in the serum, which was tentatively identified as diiodotyrosine. It is conceivable that in certain cases a genetically inborn error of metabolism of iodine could be so accentuated by iodine lack that cretinism could result. This possibility is worth exploring.

Recent studies of endemic cretins have shown that their thyroid glands may be accumulating iodine and producing thyroid hormone (24–26). A cretin with hyperthyroidism has been described (27). These results are not surprising in view of the histologic findings in the gland.

INBORN ERRORS OF METABOLISM

The synthesis of thyroid hormones by the thyroid gland involves a complex sequence of events. In all probability, the steps from the initial trapping of iodide to the final release of hormone are enzymatically controlled, and the rate at which hormone is formed and released is dependent upon the rates of each of these steps. Hypothyreosis or cretinism could result from enzymatic failure at any step in hormone synthesis or release.

Three types of familial cretinism, each characterized by a specific breakdown at a particular stage in the formation of thyroid hormone, can now be distinguished. Patients who belong to this familial grouping have in common enlarged hyperplastic thyroid glands which were noticed at birth or which developed during the first few years of life. The degree of hypothyroidism has been variable. Sporadic cretinism with goiter has been reviewed by Wilkins, Clayton and Berthrong (28).

A. *Failure of organification of iodine*

Four siblings from one family (29) and 1 patient from another (30) have been described who, while retaining an ability to trap iodide into the gland, were unable to combine it into organic residues. A similar family containing several siblings has been observed by Schultz (31). Such an interpretation was based upon the observation that a large oral dose of potassium thiocyanate caused an immediate release of I^{131} from the thyroid. This fails to occur if trapped iodide has become incorporated into tyrosine and thyronine. Further proof of the nature of the defect in 1 of these patients was offered later when direct chemical assay of the gland and metabolic study indicated that the iodine in the gland was entirely inorganic (32).

Before iodide can become attached to tyrosine, it is chemically necessary that it be oxidized to elemental iodine. It is generally agreed that an oxidase in the thyroid cell governs oxidation of trapped iodide. Although specific tests for oxidase were not made on the thyroid glands surgically removed from these cretinous patients, the experimental findings were consistent with an absence of such an oxidase. The occurrence of the same metabolic defect in 4 members of the same family suggested that the enzymatic defect was genetically determined. In this regard, it was of interest that the parents were first cousins.

B. *Failure of coupling of iodotyrosines*

Formation of several of the iodinated components of the thyroid are thought to derive from coupling of monoiodotyrosine or diiodotyrosine or both in various combinations. Thus, thyroxine occurs when two molecules of diiodotyrosine are coupled; 3-3′-diiodothyronine is derived from coupling of two molecules of monoiodotyrosine; and 3-5-3′- and 3-3′-5-triiodothyronine occur when a molecule each of monoiodotyrosine and diiodotyrosine are coupled (33).

Two sisters have been described in whom the metabolic defect may have been that coupling of iodotyrosines was much impaired (32). Both were mentally retarded and both had enlarged glands which had a high uptake and retention of I^{131}. The I^{131} could not be discharged with thiocyanate. Detailed studies were made on 1 of the patients and on the gland which

was removed surgically. Thyroxine was demonstrable in the peripheral blood, but only in very low concentration in the gland. Large amounts of monoiodotyrosine and diiodotyrosine were present in the thyroid. The gland was extremely cellular. It was postulated that minimal coupling had occurred, such as has been demonstrated in protein solutions *in vitro*, but that normally rapid enzymatically controlled coupling had failed. Only by building up a high concentration of hormone precursors was sufficient hormone produced to maintain a normal concentration of hormone in the peripheral blood. Inadequacy of compensatory hypertrophy in earlier years of life accounted for the retarded physical and mental development, but production of small amounts of hormone prevented the consequences of complete athyreosis.

C. *Lack of deiodination of iodotyrosines*

In the normal course of mobilization of triiodothyronine and thyroxine from thyroglobulin, the thyroglobulin undergoes proteolysis under the influence of a protease, and the two hormones are released for transfer into the plasma (34, 35). The fate of the monoiodotyrosine and diiodotyrosine of thyroglobulin was unappreciated until Roche (36) postulated and found a specific deiodinase in the thyroid gland which deiodinates mono- and diiodotyrosine, but not thyroxine or triiodothyronine. Deiodination of mono- and diiodotyrosine also occurs in many other tissues. The deiodinase of the thyroid removes the iodine from mono- and diiodotyrosine, and thereby prevents their appearance in the peripheral blood.

Three patients have now been studied who were unable to deiodinate diiodotyrosine and who deiodinate monoiodotyrosine only to a very limited degree (37). Two of these were brothers. All were goitrous. One of the brothers and the third patient, a 12-year-old female, were cretins. The other brother was normal mentally. In all 3 cases, when I^{131} was given, it accumulated rapidly in the thyroids, but rapidly left the glands. Chromatographic study of the serum and urine disclosed large amounts of labeled mono- and diiodotyrosine, as well as at least two unidentified iodinated substances. One of these was easily hydrolyzed into monoiodotyrosine.

If labeled mono- and diiodotyrosine are administered intravenously to normal subjects, the labeled iodine of the urine is almost entirely inorganic iodide (38, 39). Only a small fraction of the labeled iodine in the urine appears in the form of diiodotyrosine (Fig. 2). When the 3 goitrous cretins received labeled diiodotyrosine by injection, it appeared unchanged in the urine. Similarly, only a small fraction of labeled monoiodotyrosine was deiodinated. Tissue-slice studies of one of the glands removed surgically disclosed that substrate diiodotyrosine was not deiodinated, whereas slices from glands of several patients with nodular goiter readily deiodinated diiodotyrosine (40).

The foregoing observations indicated that these 3 subjects were completely unable to deiodinate diiodotyrosine and could deiodinate monoiodotyrosine only to a limited degree. Not only did these substances escape from the gland but, since deiodination could not take place elsewhere, they escaped from the body as well. The hyperplastic glands and the hypothyroid state were viewed as results of continuing loss of hormone precursors. The reasonable hypothesis seemed to be that these 3 patients lacked the deiodinase which has been demonstrated by Roche *et al.* (36). The occurrence of the same defect in 2 brothers suggested a genetic basis for the enzymatic defect. It was of interest that 5 close relatives of the third patient also had thyroid disease, but all were normally developed. Although they deiodinated diiodotyrosine, they did so less efficiently than did normal subjects. The curious rapid uptake and rapid release of I^{131} by the thyroids of certain patients with cretinism and goiter has been described by others, notably McGirr and Hutchison (41) and Hubble (42). McGirr has now reported the detection of monoiodotyrosine and diiodotyrosine in the serum of one of his goitrous cretins (43). It seems probable that McGirr and Hutchison's patients belong to

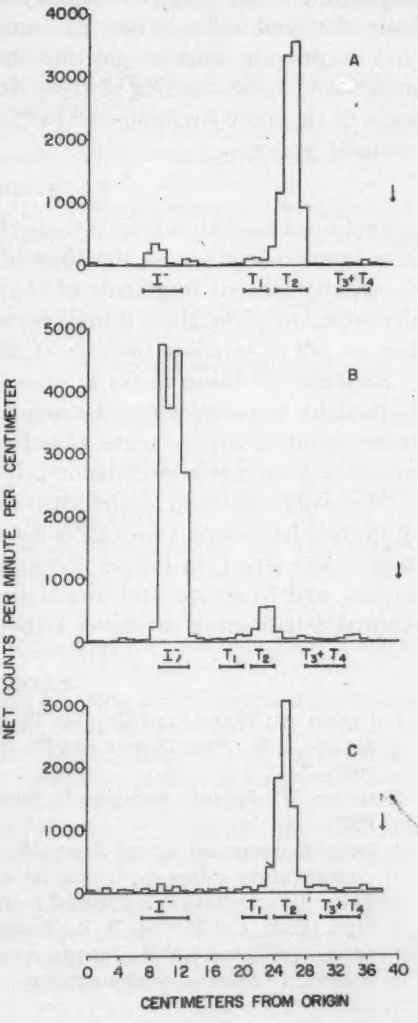

FIG. 2. Chromatographic records to show the metabolism of diiodotyrosine. Chart A is the chromatogram of the injected material. Chart B is a chromatogram of the urine of a normal subject collected one hour after intravenous administration of I^{131}-labeled diiodotyrosine. Chart C is the chromatogram of the urine of a 12-year-old goitrous female cretin one hour following administration of labeled diioodtyrosine. The bars correspond to the stained carriers on the chromatogram. I^-: Iodide. T_1: Monoiodotyrosine. T_2: Diiodotyrosine. T_3 and T_4: Thyroxine and triiodothyronine. Arrow points to the solvent front.

the same group as those described here. Werner and Block (44) have also seen a young female with goiter who was secreting large amounts of labeled mono- and diiodotyrosine into her blood.

D. *Other possible types*

It seems almost certain that in time other types of metabolic cretinism will be described in which the defect is at some other stage of hormone synthesis or release, or perhaps in transport or peripheral utilization of hormone. It is not impossible that there exists a type of cretinism corresponding to a defect at each enzymatically controlled step in the metabolic circuit of iodine. These patients are not numerically important, but they do provide some insight into the nature of iodine metabolism. More important, understanding of these defects may provide clues for study of some of the more common and baffling problems of thyroidology, such as sporadic goiter.

SUMMARY

Cretinism may arise from a multiplicity of causes. The simplest of these is congenital absence of the thyroid gland. Closely related are cases of aberrantly located fragments of thyroid tissue which represent failure of development of the gland into its normal position. Manifestations of cretinism are not so severe in patients of the latter group.

Endemic cretinism arises in association with severe endemic goiter. It is thought to occur when the iodide available to mother and fetus falls below minimal requirements. Genetic and metabolic factors have not been excluded from a role in endemic goiter.

Metabolic cretinism occurs when the primary fault is defective synthesis of thyroid hormones. Cases have been attributed to failure of iodide oxidation in the gland, to failure of coupling of hormone precursors into hormones, and to escape and loss of iodotyrosines because of the failure of normal deiodinating processes. Other types doubtless exist.

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The Endocrine Society

THE 1957 ANNUAL MEETING

The Thirty-ninth Annual Meeting of The Endocrine Society will be held in the Hotel New Yorker, New York City, Thursday, Friday and Saturday, *May 30 and 31, and June 1, 1957.*

The Committee on Local Arrangements is Dr. Rulon W. Rawson as Chairman with Drs. Earl T. Engle, Joseph W. Jailer, Warren O. Nelson, and Martin Sonenberg as members of the Committee.

All Scientific Sessions will be held in the Hotel New Yorker. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, May 31, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All members are urged to make hotel reservations immediately inasmuch as the hotels expect to be filled to capacity. Make reservations directly with the New Yorker, advising time of arrival and departure date. Make your reservations now and avoid disappointment.

Those wishing to present papers, which will be strictly limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Eleanor Venning, Royal Victoria Hospital, Montreal, Quebec, Canada, *not later than February 1, 1957. It is imperative that the abstracts be informative and complete with results and conclusions—not a statement that these will be presented at the meeting*—in order that they may be of reference value and suitable for printing in the program and journals of the Society. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. Reference, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each nonmember author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of nonmembers who are introduced, *i.e.*,

who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.

Line 3. Institution of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter perfect, since there will be no opportunity for proof reading by authors.

THE 1957 AWARDS

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors.

MEDAL OF THE ENDOCRINE SOCIETY

In 1954 the Council of the Society voted to establish a medal and an honorarium of $1,000 to be given to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada. Dr. Carl R. Moore was the recipient in 1955 and Dr. Frederick L. Hisaw in 1956.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishments of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; 1945—Dr. Jane A. Russell; 1946—Dr. Martin M. Hoffman; 1947—Dr. Choh Hao Li; 1948—Dr. Carl Heller; 1949—Dr. George Sayers; 1950—Dr. Oscar M. Hechter; 1951—Dr. Albert Segaloff; 1952—Dr. Seymour Lieberman; 1953—Dr. Sidney Roberts and Dr. Clara Szego (Mrs. Roberts); 1954—Dr. Isadore M. Rosenberg; 1955—Dr. Jack Gross; 1956—Dr. Alfred M. Bongiovanni. Prior to 1952 the Award was $1,200. It is now $1,800. If within twenty-four months of the date of the award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

THE AYERST AND THE SQUIBB FELLOWSHIPS

The Ayerst Fellowship was established in 1947 and the Squibb Fellowship in 1956. They are designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. Each Fellowship is awarded on alternate years and the stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

THE SCHERING AND THE UPJOHN SCHOLARS OF THE ENDOCRINE SOCIETY

The Council of The Endocrine Society has established a category of Scholars. These grants have been made available through the generosity of the Schering Corporation and the Upjohn Company, and will be awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work either in this country or abroad.

The awards will not exceed $2,500 annually for each individual and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Medal of the Endocrine Society; the Ciba Award; and the Ayerst and the Squibb Fellowships may be made by any member of The Endocrine Society. They should be submitted on forms which may be obtained from the Office of the Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma. Completed nominations should be returned to the Secretary not later than *November 1* each year.

Proposals for appointments as Scholars of The Endocrine Society should

be made in writing by the individual, and addressed to the Secretary of the Society. They should be submitted by *November 1* each year.

The Awards Committee will meet in November and notice of awards to successful nominees and applicants will be made not later than December 1.

The American Goiter Association

THE 1957 ANNUAL MEETING

The next Annual Meeting of The American Goiter Association will be held in the Statler Hotel, New York City, on *May 28, 29 and 30, 1957.*

THE VAN METER PRIZE AWARD FOR 1957

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held in the Hotel Statler, New York, May 28, 29 and 30, 1957, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, *not later than January 15, 1957.* The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

RECIPIENTS OF AWARDS FOR 1956

In 1921 a group of medical men began meeting informally under the title of the Illinois Clinical Club with Dr. E. P. Sloan as their leader. This group visited medical clinics and hospitals throughout the United States, where they noted that in many medical centers there was lack of recognition of the presence of goiter in the area. To stimulate research as to the cause of goiter, this informal clinical club brought together men from all over the United States and in 1923 formed The American Association for the Study of Goiter. The purpose of the new group was to establish a forum where all subjects pertaining to goiter could be presented and fully discussed, to publish the results of their deliberations, and to hold meetings in different sections of the country to stimulate interest in the problem of goiter. In 1948 the name was changed to The American Goiter Association.

RECIPIENT OF VAN METER PRIZE

One of the early members of the Association, Dr. Seymour D. Van Meter of Denver, Colorado, offered a prize of $300 to be awarded to the essayist presenting the best work on the subject of "goiter—especially its basic cause." This award was first given in 1930 and was donated annually by Dr. Van Meter until his death in 1934. In recognition of his generosity, and because of his many contributions to the Association, the award was named The Van Meter Prize Award following the death of its originator. The award has been offered annually with the exception of the years 1943, 1944 and 1945. It has also been the custom to acknowledge the two next best essays with the accolade, "Honorable Mention."

Essays submitted in the competition each year may deal with basic research into the function of the thyroid gland or may reflect clinical studies dealing with this organ. Over the years manuscripts have been received from a dozen foreign countries as well as the United States, and foreign investigators are numbered among the winners of the award.

Each year a committee of at least five members of the Association representing clinicians in the fields of medicine and surgery together with members working in basic chemical, physical or physiological research have been responsible for judging the essays and selecting the winners.

The winner of this high honor in 1956 was Dr. Jamshed R. Tata for his essay entitled, "Studies on an Iodinated Protein in the Serum of Patients with Cancer of the Thyroid."

Dr. Tata has been a visiting research fellow of the Sloan-Kettering Institute since November 1954. His sphere of research has centered around the nature of iodinated compounds in patients with thyroid cancer and on the metabolism of thyroid hormones in the brain. Dr. Tata was born in

India twenty-six years ago and received his B.S. degree from the University of Bombay in 1949. In his specialty of biochemistry Dr. Tata continued his studies at the University of Bombay and was granted the degree of Master of Science (M.S.) in 1951. He then pursued his post-graduate training in Paris where the University of Paris awarded him the degree of Doctor of Science (D. Sc.) in 1954.

Dr. Tata's research studies have concerned the biochemistry of malarial parasites, in India, and the metabolism of thyroid hormones, in the Collège de France where he was the pupil of Professors Jean Rode and Raymond Michel. Since 1954 he has been a Research Fellow at Sloan-Kettering Institute, New York.

The Honorable Mention awards were granted by the Association this year to *Dr. A. F. Phillips,* Addenbrooke's Hospital, Cambridge, England for his paper entitled, "The Choice of a Radioactive Isotope for Treatment of Carcinoma of the Thyroid," and to *Dr. Chalmers L. Gemmill,* University of Virginia School of Medicine, Charlottesville, Virginia, for his paper entitled, "The Metabolic Activity of 3,3′-Diiodothyronine and 3,3′-Diiodo-5-bromothyronine."

RECIPIENT OF AWARD OF MERIT

In 1953, when the American Goiter Association met in Chicago at the Drake Hotel, a benefactor whose identity has remained anonymous gave an award which was to be repeated three years. The deed of gift specified that the Award should be known as the American Goiter Association Award of Merit and that the recipient must be a member of the Association under 45 years of age who had contributed in an outstanding manner to our knowledge of the thyroid gland. The award was enhanced by an honorarium of $1000 per annum.

All winners of this honor have been selected by a committee of the Association, ineligible themselves to receive the Award but well qualified to judge the merits of those nominated for it. The first recipient was Dr. Brown M. Dobyns, now the new President of our Association. The second winner was Dr. Alexander Albert, a member of our Executive Council.

At the 1956 meeting in Chicago, the third and final award contained in the original gift was presented. *The winner was Dr. Douglas S. Riggs.*

Dr. Riggs was born of missionary parents in Turkey in 1914. He returned to this country, where Yale University granted him a B.S. degree in 1936. Three years later, in 1939, the School of Medicine at Yale gave him the degree, Doctor of Medicine.

Following his graduation, Dr. Riggs began his career immediately in physiology and pharmacology. From 1942 to 1946 he was the Biochemist at Fairfield State Hospital in Connecticut, and during this same period he

was an instructor in pharmacology at his Alma Mater. In 1946 he became an instructor in pharmacology at Harvard University, where he rose to the rank of assistant professor in 1951. In 1954, Dr. Riggs was made Professor and Head of the Department of Pharmacology, University of Buffalo School of Medicine, a position he now holds.

Along with his academic responsibilities, Dr. Riggs has found time to produce more than fifty publications. His particular contributions have centered around the determination, distribution and behavior of blood iodine in health and in disease. For these additions to our knowledge of the function of the thyroid gland, Dr. Riggs has been honored with the Award of Merit.

RECIPIENT OF AWARD FOR MERITORIOUS SERVICE

Samuel F. Haines, M.D. was born in Mantorville, Minnesota, and received his early education in Rochester. His collegiate work was rewarded by Harvard in 1915 with a B.S. degree. (This Harvard class is famous for the number of outstanding citizens it produced.) Harvard granted Dr. Haines the M.D. degree in 1919, to which the University of Minnesota added an M.S. in medicine in 1929.

Dr. Haines collaborated with F. D. Williams to produce his first article on the thyroid gland in 1925. Since then his bibliography numbers nearly a hundred publications.

In 1931, he became a member of this Association, which he has served as Chairman of the Program Committee three times and in 1954 as Chairman of the Publications Committee. He was on the Executive Council in 1940 and from 1947 through 1951. In 1949–50, he was the Association's President. During his career he has contributed through his membership and participation to more than ten county, state and national medical societies. He has achieved prominence on the editorial boards of well known medical journals.

In 1924, Dr. Haines entered the Mayo Clinic as an instructor. Since then he has held many positions of importance, including Chairman of the Board of Governors. At present he is the Senior Consultant on metabolic diseases.

In addition to these academic accomplishments, Dr. Haines has found time to become a proficient gardener, a first class painter in water colors and an enthusiastic dry-fly fisherman. Bird watching finds him in the country side at hours when many of his colleagues are still asleep.

Early in his association with the thyroid gland, Dr. Haines was the ardent student and favorite assistant of the illustrious Henry Plummer. Over the years, Sam Haines has numbered among his friends, the thyroidologists of the world. Whether the contact was daily at his work or

annually at a meeting, all who know Samuel Haines respect and admire him for his honesty and vision.

For his continuing interest in the American Goiter Association and his many contributions to our knowledge, by unanimous decision of the members, he was awarded this certificate for long and meritorious service.

NEW YORK HEART ASSOCIATION CONFERENCE

The New York Heart Association is planning a one-day conference on "Atherosclerosis and Coronary Heart Disease" to be held at the *Waldorf-Astoria, New York, Tuesday, January 15, 1957.* Dr. Robert L. Levy is chairman of the steering committee. Speakers will include Dr. Paul D. White, Dr. E. Cowles Andrus, Dr. Herman E. Hilleboe, and Dr. Ancel Keyes. Many other prominent cardiologists and notables in the public health field are also expected to participate.